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CONTENTS

NUMBER 93, OCTOBER 1930

An Investigation into the Gastric Secretion of a Hundred Normal Persons over the Age of Sixty. By Daniel T. Davies and T. G. Illtyd James . . 1

Bundle-Branch Block. A Clinical and Histological Study. By Ian G. W. Hill. With Plates 1–3 15

A Clinical Study of Bronchial Carcinoma. By James Maxwell and W. A. Nicholson 29

Spontaneous Cardiac Rupture. A Review of Forty-six Cases. By E. H. Beresford and C. J. C. Earl. With Plates 4–6 55

Paroxysmal Auricular Fibrillation. A Record of Two Hundred Patients. By John Parkinson and Maurice Campbell 67

Critical Review: The Harmful Effects of Irradiation (X-Rays and Radium). By Humphry Rolleston 101

NUMBER 94, JANUARY 1931

The Effect of Oils on Gastric Secretion and Motility. By W. Morrell Roberts 133

The Clinical Interpretation of the Intradermal Tuberculin Reaction. By Alan Moncrieff 153

Intestinal Carbohydrate Dyspepsia. By Arthur F. Hurst and F. A. Knott. With Plates 7–8. 171

The Hypochlorhydria of Asthma in Childhood. By George W. Bray . . 181

A Radiographic Study of the Coronary Arteries in Health and Disease. By E. Wyn Jones. With Plates 9–15 199

The Importance of Familial Achlorhydria in the Aetiology of Pernicious Anaemia. By John Frederick Wilkinson and William Brockbank . . 219

The Conception of 'Nephrosis'. Observations on Three Fatal Cases. By T. Izod Bennett, E. C. Dodds, and J. D. Robertson. With an Account of the Histological Changes by S. L. Baker. With Plates 16–18 . . 239

The Sugar-Content of the Blood in Elderly People. By F. W. Marshall . . 257

NUMBER 95, APRIL 1931

The Blood-platelet: Its Clinical Significance. By W. MacKay . . . 285

Some Observations on the Circulatory Mechanism in Marathon Runners. By Crighton Bramwell and Reginald Ellis. With Plates 19–20 . . . 329

Urticaria: Some Observations upon the Vascular Reactions in the Skin. By Kenneth E. Harris. With Plate 21 347

Generalized Myositis Fibrosa. By J. A. G. Burton, John Cowan, and John Fleming 369

Inorganic Constituents of Cerebrospinal Fluid. I. Calcium and Magnesium. By Robert Alexander McCance and Elsie Watchorn 371

Arsenobenzol Purpura. With a Short Description of Four Cases. By J. Bamforth and J. St. G. Elk[illegible]ton 381

Critical Review: The Metabolism of Calcium and Phosphorus and the Parathyroids in Health and Disease. By Donald Hunter 393

NUMBER 96, JULY 1931

Studies on Achlorhydria and Anaemia. By Daniel T. Davies. With Plate 22 447

The Elimination of Focal Sepsis in the Treatment of Parathyroid Tetany. By G. C. Linder, C. F. Harris, and F. R. Fraser 469

Right Bundle-Branch Block: An Analysis of the Clinical Records of Fifty-six Cases with Typical Electrocardiograms. By S. B. Boyd Campbell and S. I. Turkington. With Plates 23–24 481

The Clinical and Epidemiological Characteristics of Variola Minor and its Differential Diagnosis. By Chris. J. McSweeney 487

The Size and Shape of the Heart in Goitre. By John Parkinson and Harold Cookson. With Plates 25–29 499

Functional Disorders of the Colon. By Edmund I. Spriggs. With Plates 30–34 533

The Excretion of Creatinine by the Human Kidney in Health and in Nephritis. By C. L. Cope 567

Critical Review: Intracranial Tumours. By F. M. R. Walshe 587

Proceedings of the Association of Physicians of Great Britain and Ireland. Twenty-fourth Annual General Meeting . . . . . *at end*

INDEX OF CONTRIBUTORS

BAKER, S. L. The Conception of 'Nephrosis'. Observations on Three Fatal Cases. With an Account of the Histological Changes. With Plates 16–18 239

BAMFORTH, J. Arsenobenzol Purpura. With a Short Description of Four Cases 381

BENNETT, T. I. The Conception of 'Nephrosis'. Observations on Three Fatal Cases. With an Account of the Histological Changes. With Plates 16–18 239

BERESFORD, E. H. Spontaneous Cardiac Rupture. A Review of Forty-six Cases. With Plates 4–6 55

BRAMWELL, C. Some Observations on the Circulatory Mechanism in Marathon Runners. With Plates 19–20 329

BRAY, G. W. The Hypochlorhydria of Asthma in Childhood . . . 181

BROCKBANK, W. The Importance of Familial Achlorhydria in the Aetiology of Pernicious Anaemia 219

BURTON, J. A. G. Generalized Myositis Fibrosa 369

CAMPBELL, M. Paroxysmal Auricular Fibrillation. A Record of Two Hundred Patients 67

CAMPBELL, S. B. B. Right Bundle-Branch Block: An Analysis of the Clinical Records of Fifty-six Cases with Typical Electrocardiograms. With Plates 23–24 481

COPE, C. L. The Excretion of Creatinine by the Human Kidney in Health and in Nephritis 567

COOKSON, H. The Size and Shape of the Heart in Goitre. With Plates 25–9 499

COWAN, J. Generalized Myositis Fibrosa 369

DAVIES, D. T. An Investigation into the Gastric Secretion of a Hundred Normal Persons over the Age of Sixty 1

——— Studies on Achlorhydria and Anaemia. With Plate 22 . 447

DODDS, E. C. The Conception of 'Nephrosis'. Observations on Three Fatal Cases. With an Account of the Histological Changes. With Plates 16–18 239

EARL, C. J. C. Spontaneous Cardiac Rupture. A Review of Forty-six Cases. With Plates 4–6 55

ELKINGTON, J. ST. G. Arsenobenzol Purpura. With a Short Description of Four Cases 381

ELLIS, R. Some Observations on the Circulatory Mechanism in Marathon Runners. With Plates 19–20 329

FLEMING, J. Generalized Myositis Fibrosa 369

FRASER, F. R. The Elimination of Focal Sepsis in the Treatment of Parathyroid Tetany 469

HARRIS, C. F. The Elimination of Focal Sepsis in the Treatment of Parathyroid Tetany 469

HARRIS, K. E. Urticaria: Some Observations upon the Vascular Reactions in the Skin. With Plate 21 347

HILL, I. G. W. Bundle-Branch Block. A Clinical and Histological Study. With Plates 1–3 15

HUNTER, D. Critical Review: The Metabolism of Calcium and Phosphorus and the Parathyroids in Health and Disease 393

HURST, A. F. Intestinal Carbohydrate Dyspepsia. With Plates 7–8 . . 171

JAMES, T. G. I. An Investigation into the Gastric Secretion of a Hundred Normal Persons over the Age of Sixty 1

JONES, E. W. A Radiographic Study of the Coronary Arteries in Health and Disease. With Plates 9–15 199

KNOTT, F. A. Intestinal Carbohydrate Dyspepsia. With Plates 7–8 . . 171

LINDER, G. C. The Elimination of Focal Sepsis in the Treatment of Parathyroid Tetany 469

MACKAY, W. The Blood-platelet: Its Clinical Significance 285

MARSHALL, F. W. The Sugar-Content of the Blood in Elderly People . . 257

MAXWELL, J. A Clinical Study of Bronchial Carcinoma 29

MCCANCE, R. A. Inorganic Constituents of Cerebrospinal Fluid. I. Calcium and Magnesium 371

MCSWEENEY, C. J. The Clinical and Epidemiological Characteristics of Variola Minor and its Differential Diagnosis 487

MONCRIEFF, A. The Clinical Interpretation of Intradermal Tuberculin Reaction 153

NICHOLSON, W. A. A Clinical Study of Bronchial Carcinoma 29

PARKINSON, J. Paroxysmal Auricular Fibrillation. A Record of Two Hundred Patients 67

——————— The Size and Shape of the Heart in Goitre. With Plates 25–9 499

Proceedings of the Association of Physicians of Great Britain and Ireland. Twenty-fourth Annual General Meeting . . . . . *at end*

ROBERTS, W. M. The Effect of Oils on Gastric Secretion and Motility . . 133

ROBERTSON, J. D. The Conception of 'Nephrosis'. Observations on Three Fatal Cases. With an Account of the Histological Changes. With Plates 16–18 239

ROLLESTON, H. Critical Review: The Harmful Effects of Irradiation (X-Rays and Radium) 101

SPRIGGS, E. I. Functional Disorders of the Colon. With Plates 30–4 . . 533

TURKINGTON, S. I. Right Bundle-Branch Block: An Analysis of the Clinical Records of Fifty-six Cases with Typical Electrocardiograms. With Plates 23–24 481

WALSHE, F. M. R. Critical Review: Intracranial Tumours 587

WATCHORN, E. Inorganic Constituents of Cerebrospinal Fluid. I. Calcium and Magnesium 371

WILKINSON, J. F. The Importance of Familial Achlorhydria in the Aetiology of Pernicious Anaemia 219

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AN INVESTIGATION INTO THE GASTRIC SECRETION OF A HUNDRED NORMAL PERSONS OVER THE AGE OF SIXTY [1]

By DANIEL T. DAVIES and T. G. ILLTYD JAMES

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The study of the variations in the gastric secretion in normal healthy adults, and also in diseased conditions, has resulted in a better understanding of gastric function. A similar study into the gastric secretion of early life, both in health and disease, has furnished much information, especially with regard to the possible origin of achlorhydria, but similar investigations on the gastric secretion in old age have been singularly few. In a study such as this many points arise which deserve attention, but of these the incidence of achlorhydria at this stage of life is possibly the first. It is interesting to recall the findings of Wright (1), who examined 250 normal children between the ages of 6 and 15 years, when he found a frequency of 1·6 per cent. of achlorhydria, and also of Hertz, Chievitz, and Andersen (quoted by Faber (2)), who examined 127 healthy children, to find 'no evidence of a constitutional or a congenital origin for achlorhydria'. The series of 100 young healthy students of Bennett and Ryle (3) yielded four who showed achlorhydria, and in this series 80 per cent. fell into normal limits. A higher frequency of achlorhydria can be expected with advancing years, but unfortunately the methods of the few authors who have investigated the problem at this time of life are not uniform, and comparison with Bennett and Ryle's standard series cannot be made. Seidelin (4) found absent or greatly diminished secretion in 40 per cent. of the working classes above the age of 50 at Copenhagen, while Dedichen (5) reported achlorhydria in sixty-six out of a series of ninety-nine healthy persons between the ages of 67 and 92 years. But the method of analysis used by the latter observer was the one-hour method of Ewald, and the increased occurrence of achlorhydria in this series can be readily accounted for by his method of investigation.

The present study was begun with the following objects in view.

1. To determine the frequency of achlorhydria in the latter decades, and by the estimation of gastric ferments to distinguish the cases of achlorhydria from true cases of achylia.

[1] Received June 20, 1930.

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2. To ascertain the effect of histamine on the gastric secretion in those cases presenting achlorhydria by the ordinary method of analysis.

3. To observe the relationship of the above findings to the blood condition.

All the individuals selected for this investigation were in good health, and in none was there any previous digestive ill-health. Varying degrees of senility existed, and all possessed some arterial sclerosis, whilst chronic bronchitis was almost a constant finding. The ages varied between 60 and 95; 47 were males and 53 were females.

Methods of Investigation.

1. *Clinical examination.* In addition to obtaining a history of freedom from any digestive symptoms the following points were specially noted. *The appetite*: whether good, fair, poor, or bad. *The tongue*: whether rough and possessing papillae or smooth and glazed. The presence or absence of anaemia. The presence or absence of dysphagia. The condition of arteries and blood-pressure.

2. *Gastric analysis* by the usual fractional method, using gruel as the meal and noting the usual findings.

3. *Gastric analysis* after histamine injection in those cases which showed achlorhydria by the ordinary method.

Histamine in the form of histamine hydrochloride was injected subcutaneously after the resting juice had been withdrawn. The average dose employed was 0·5 mg., and in all of the cases so injected no untoward symptoms were observed, a transient flush being the only observable effect on the patients. The juice was aspirated at fifteen minutes' and at thirty minutes' interval following the injection. The volume of the juice secreted and the free and total acid values were noted in the three samples. In addition to the acid titration the estimation of the gastric ferments was also conducted on this series. The method employed for this purpose was that of Fuld (6), and although all methods for pepsin estimation are open to criticism, this method seemed to be the most practical and gave comparative results. All dilutions of the gastric juice were made with N/30 HCl, and a 0·1 grm. of edestin in N/30 HCl was used as the standard protein for digestion. All dilutions of the gastric juice were incubated for one half hour at 37° C.

4. *Blood counts* were performed on all cases showing achlorhydria, and the results of these are tabulated and compared with those obtained in cases showing an abundant secretion of HCl.

The gastric response to the ordinary gruel meal of the hundred cases can be divided conveniently for the purpose of study into the usual four groups. A. *Achlorhydria*—32 of all cases. B. *Low secretion of HCl*—i.e. figures below 10 c.c. N/10 NaOH—12 of all cases. C. *Normal secretion of HCl*—i.e. figures between 10 and 50 c.c. N/10 NaOH—43 of all cases. D. *High secretion of HCl* —i.e. figures above 50 c.c. N/10 NaOH—13 of all cases.

Results of the Investigation.

Taking the series as a whole the most striking departure from the normal is the high incidence of achlorhydria—32 per cent. It was also observed that the gruel frequently remained unchanged in the aspirated fractions, showing no evidence of digestion both in the acid and anacid cases, and this was specially marked in the first hour-and-half period. Associated with this comparatively common finding was smallness in volume of the juices recorded. It may be that the inhibition of secretion observed in these cases was due to the psychical influence of the test meal examination, for none of the patients had such an experience before. The various groups will be taken in order and compared.

A. *Achlorhydria.*

Thirty-two of the series of 100 showed no free HCl in the gastric secretion by means of the ordinary fractional analysis with the gruel meal. These can be divided into two groups, namely, apparent achlorhydria: those showing HCl secretion after injection of histamine—13 of all cases; and true achlorhydria: those showing no hydrochloric acid after injection of histamine—14 of all cases. Unfortunately 5 of the above 32 were unable to be examined again with histamine injection, 3 of them having died and 2 having returned home. Of the 32, 12 were males and 20 were females. The blood-pressure varied between 110 mm. Hg and 202 mm. Hg systolic, and varying degrees of arterial sclerosis were found in all of the cases. The 5 incompletely-investigated cases will be taken separately.

Apparent achlorhydria was present in 13 of the 32 cases, i.e. after the subcutaneous injection of histamine hydrochloride HCl secretion appeared in the gastric juice in titratable amounts. Of these 13 the appetite was good in 11 and 'fair' in 2. In 1 only was there any change observable in the tongue, the mucous membrane being glazed and atrophic in Case No. 47, an old woman of 81. Dysphagia was not elicited as a symptom in any of the 13 cases, but in several of the cases a degree of pallor was noted clinically. The ages varied between 60 and 83, and 10 were females and 3 were males.

The resting juice varied in volume between 5 and 20 c.c., and in none of the cases was the odour observed to be offensive. In only 2 was mucus observed to be present in excessive degree. The disparity between total acid values and the base line varied between 5 and 20 c.c. N/10 NaOH, except in 1 case, in which it was 30. The emptying rate varied between 1 and 2¼ hours, a more rapid rate being observed in this series than in the cases showing HCl.

In all of these cases free HCl was found after histamine injection. In addition to noting the amount of HCl secreted the volume of the juice was also noted. Variation in HCl values from 64 to 8 c.c. N/10 NaOH were obtained, and a rough parallel was observed between the amount of HCl secreted and the volume of the juice.

In 7 of the cases the pepsin content of the juices was also estimated. In none of these cases was there complete absence of pepsin, indeed some possessed a high content of the ferment. These cases will be referred to in order.

Case 1. An old woman of 83, who showed achlorhydria in the first analysis, and who showed no free HCl until the 30-minutes' specimen after histamine, possessed pepsin both in the resting juice and in the 15-minutes' specimen to values of 64 and 32 units respectively (i. e. $\frac{1}{32}$ c.c. and $\frac{1}{16}$ c.c. of gastric juice were able to digest the standard Edestin solution under standard conditions), and in the last specimen with a free HCl value of 8 c.c. N/10 NaOH showed a peptic activity of 250 units.

Case 15. A female aged 65—who had also previously shown achlorhydria—after histamine showed a HCl secretion equivalent to 50 c.c. N/10 NaOH in the first 15-minute period, and in the 30-minute specimen equivalent to 26 c.c. N/10, NaOH, with a corresponding peptic activity of 512 units.

Case 31. A male, aged 67, showed an unusually high pepsin content even in the resting juice, although this contained no free HCl, and following the injection of histamine, when the free acidity reached a height of 44 c.c., N/10 NaOH the pepsin rose to a figure of 1020 units, i. e. $\frac{1}{510}$ c.c. of gastric juice was able to digest the standard problem.

Case 82. A female, aged 75, with an acidity of 20 c.c. N/10 NaOH, showed a pepsin content of 500 units in the 30-minute specimen and in the resting juice of 60 units.

Case 84. A female of 72 showed similar figures, the increasing pepsin content being parallel with the increase in the free acid secretion, i.e.

Free HCl	0	22	42
Pepsin Units	16	128	250

Case 96. A male, aged 60, in addition to showing little free HCl secretion following histamine (15 c.c. N/10 NaOH in the 30-minute specimen) was free of pepsin until the last specimen, which had a low pepsin value of 32.

Case 99. A female, aged 70, showed no ferment in the resting juice and only small values in the 15-minute and 30-minute specimens, in spite of a fairly good secretion of HCl.

Free HCl	0	10	40
Pepsin Units	0	32	16

True achlorhydria was present in 14 of the 32 cases which had previously shown achlorhydria and still showed absence of HCl after the subcutaneous injection of histamine hydrochloride. The ages of this group varied between 61 and 86; 7 were females and 7 were males. In 10 of the cases some degree of anaemia was observed clinically, and in 4 of the cases the tongue was noted as being glazed and atrophic in surface. The appetite was only impaired in 1 and none complained of dysphagia.

The resting juice varied in volume between 5 and 30 c.c. and mucus was noted to be excessive in only 3. The odour was not offensive in one, and in all of the cases the disparity between the total acid line and the base line was less than a value of 20 c.c. N/10 NaOH, except in 1, in which it was 30. The emptying rate varied between $\frac{1}{2}$ and $2\frac{1}{4}$ hours, the majority emptying within $1\frac{1}{2}$ hours. Bile was absent from all the samples. Of these 14, 3 of the cases were injected a second time, but again no free HCl was demonstrable.

TABLE I.

Achlorhydria with HCl Secretion After Histamine Injection.—Apparent Achlorhydria.

								Ordinary Gastric Analysis.				Gastric Analysis with Histamine Injection.								
												Resting Juice.		15 Minutes.			30 Minutes.		
Case No.	Age.	Sex.	Appetite.	Tongue.	Red Cells.	Hb %.	White Cells.	Volume Resting Juice.	Mucus.	Max. Total Acidity.	Emptying Rate in Hrs.	Volume.	Peptic Units.	Volume.	HCl.	Peptic Units.	Volume.	HCl.	Peptic Units.
								c.c.				c.c.		c.c.					
1	83	F	Good	Normal	4·5	50	7,500	20	+ + +	8	2¼	17	64	6	0	32	7	8	250
15	65	F	Fair	„	4·5	50	11,200	10	Nil	18	2¼	20	—	30	50	—	10	26	512
25	75	F	Good	„	5·48	80	16,200	5	+	16	1¼	10	—	30	50	—	15	62	—
31	67	M	„	„	4·8	75	9.200	20	Nil	12	2	20	520	25	25	500	30	44	1020
46	60	F	„	„	4·3	78	8,200	10	„	12	1½	5	—	5	16	—	10	22	—
47	81	F	„	Smooth	4·4	60	8,400	10	„	20	1	8	—	15	64	—	10	45	—
51	82	F	„	Normal	5·5	70	8,000	10	„	15	1¼	20	—	25	8	—	10	0	—
63	61	F	„	„	3·8	60	10,000	15	+ + +	16	1¼	15	—	10	30	—	20	45	—
72	76	M	„	„	4·75	86	8,000	12	Nil	12	1	5	—	6	20	—	8	0	—
82	75	F	Fair	„	4·2	50	6,800	4	„	20	2¾	5	60	10	10	—	15	20	500
84	72	F	Good	„	4·5	60	7,000	8	„	8	1½	12	16	20	22	128	25	42	250
96	60	M	„	„	4·6	75	10,000	15	„	30	2	10	Nil	15	0	Nil	25	15	32
99	70	F	„	„	4·5	85	8,400	5	„	12	1¾	8	Nil	13	10	32	15	40	16

TABLE II.

Achlorhydria After Histamine Injection.—True Achlorhydria.

Case No.	Age.	Sex.	Appetite.	Tongue.	Red Cells.	Hb %.	White Cells.	Ordinary Gastric Analysis.					Gastric Analysis with Histamine Injection.									
								Volume Resting Juice.	Mucus.	Max. Total Acidity.	Emptying Rate in Hrs.	Resting Juice.			15 Minutes.			30 Minutes.			
												Volume.	Peptic Units.	Volume.	HCl.	Peptic Units.	Volume.	HCl.	Peptic Units.		
								c.c.				c.c.		c.c.			c.c.				
10	65	F	Good	Smooth	4·0	70	8,000	15	+ + +	5	1½	10	—	6	0	—	6	0	512		
18	72	M	,,	,,	5·2	80	9,000	30	Nil	20	2¼	9	Nil	13	0	—	16	0	16		
21	68	F	,,	Normal	4·6	62	7,400	10	,,	12	1½	6	64	10	0	64	10	0	64		
26	77	M	Fair	Smooth	5·0	80	9,800	10	+ +	8	1	9	24	7	0	—	9	0	64		
28	67	F	Good	Normal	4·0	70	7,500	20	Nil	8	1	10	Nil	10	0	120	8	0	16		
39	75	M	,,	,,	3·8	65	8,400	5	+ + +	20	1¾	8	,,	8	0	16	4	0	16		
42	73	F	,,	,,	3·4	60	7,600	26	Nil	10	1¾	10	64	16	0	64	20	0	128		
67	68	M	,,	,,	5·5	90	9,000	15	,,	20	1¾	6	8	15	0	64	7	0	128		
74	61	F	,,	,,	5·0	70	8,000	15	,,	9	2	10	32	12	0	64	15	0	64		
79	75	F	,,	Smooth	3·7	84	8,500	10	+ + +	20	1½	15	—	30	0	—	30	0	—		
88	75	F	,,	Normal	4·5	60	8,000	30	Nil	15	1¾	8	8	8	0	16	7	0	8		
92	86	M	,,	,,	3·8	50	9,800	8	,,	30	1	5	Nil	5	0	8	5	0	Nil		
93	68	M	,,	,,	4·5	60	8,700	5	,,	10	1¾	5	—	5	0	—	10	0	64		
97	76	M	,,	,,	3·7	65	10,000	5	,,	20	1	2	—	10	0	16	12	0	Nil		

The volumes both of the resting juice and the specimens obtained after histamine were observed to be small, and in 12 of the 14 were less than 20 c.c. In the remaining 2 the volumes reached 20 and 30 c.c. respectively after histamine.

The pepsin content was estimated in 13 of the cases, and in all of these it was found in varying concentration.

The highest figure recorded in this group was that of Case No. 10—a female aged 65—who showed a value of 512 units in the 30-minute specimen, although, as in all the cases of this group, no free HCl was present. The lowest ferment content was found in Case No. 92, a male aged 82, in which the resting juice contained no pepsin, while the specimen withdrawn 15 minutes after histamine contained the ferment only to a value of 8 units. A low figure was also obtained in Case No. 97, a male aged 76, and that only after stimulation with histamine. Six of the 13 cases showed definite values for pepsin in the resting juice and 4 possessed none. All of the cases showed a better secretion of pepsin after the injection of histamine than in the resting juice.

Five cases showed achlorhydria with the ordinary fractional analysis only, consequently no knowledge is forthcoming whether they would have yielded free HCl or not after histamine injection. Table III gives the main details about these cases.

TABLE III.

Case No.	Age.	Sex.	Appetite.	Tongue.	Red Cells.	Hb %.	White Cells.	Volume Resting Juice.	Mucus.	Max. Total Acidity.	Empty Rate.
											Hrs.
3	77	F	Good	Smooth	5·0	50	16,000	15	+ + +	12	1⅓
4	81	F	„	Normal	4·0	30	5,000	10	Nil	10	1½
9	80	M	„	Smooth	4·5	80	8,000	8	Nil	8	1¼
16	64	F	„	Normal	4·5	75	8,000	20	+ +	5	1¼
19	68	M	„	Normal	—	—	—	30	Nil	20	1½

The blood findings. Of the 13 cases of subdivision I, which showed HCl response following histamine injection, all had red cell values above 4·0 million but one—Case 63—a female, aged 61, who showed a red cell count of 3·8, and 6 of the cases showed an Hb percentage of 60 or below. While, of the 14 cases that showed no free HCl after histamine, 7 showed red cell counts between 3 and 4 million and 4 a haemoglobin percentage of 60 or below. In only 1 of the 14 cases was the colour index above 1, and that was found in Case 79, in which the red cell count was 3·7 million and the Hb per cent. 84. The lowest red cell count noted was 3·4 million with an Hb of 60 per cent in Case No. 42. The blood-film of this case showed many red cells larger than normal—macrocytes—but no nucleated forms. In only 2 others was this tendency to larger than normal forms noted, i.e. in Cases 92 and 97. In the 3 cases the red cells were well stained and filled with haemoglobin. Many of the

other films showed central pallor, but no other abnormal feature. Two of the 5 incompletely investigated series showed haemoglobin values of 50 and 30 per cent.

B. *Low Secretion of HCl.*

In 12 of the cases the HCl values ranged above 0 and below 10 c.c. N/10 NaOH. In this group the appetite was noted as good in all except 1, in whom it was poor. No anaemia was observed, and in 1 only was the tongue smooth and glazed. The youngest was 60 and the eldest 83. Seven were females and 5 were males. The blood-pressure varied between 110 mm. Hg and 220 mm. Hg systolic, and varying degrees of arterial sclerosis were found in all the cases.

The volume of the resting juice varied between 5 and 20 c.c. In 5 of the cases mucus was noted as excessive. In 11 of the 12 no free HCl was found in the resting juice, but the odour of the resting juice was normal in all. The maximal disparity between the free and total acidity was found in Case No. 32, a woman of 81 years, which showed a disparity of 30 in the resting juice.

The emptying rate varied between 1 and 3 hours. Bile was present in 7 of the cases in some or all of the specimens withdrawn.

As the figures obtained in this series yield little in the way of information they will not be tabulated.

C. *Normal Secretion of HCl.*

Forty-three of the cases showed a gastric secretion falling within normal limits, i. e. the HCl values ranged between 10 and 50 c.c. N/10 NaOH. In the 43 cases the appetite was noted as being good, no history of dysphagia was obtained, and the tongue possessed papillae and was rough in surface in all the cases but one. Clinically none of the cases was anaemic, and many were ruddy in complexion. The ages of the group varied between 61 and 90, and 22 were males and 21 were females. Chronic bronchitis was almost invariably present (as indeed in all the other groups), and arteries of varying degrees of sclerosis were found. The blood-pressure of the individual cases varied between 125 mm. Hg systolic and 225 mm. Hg systolic.

The volume of the resting juice ranged between 5 and 30 c.c.; mucus was found excessive in only 5, and in the others either present in only traces or not at all. The odour was not found to be unpleasant in any.

In 23 of the 43 cases no free HCl was found in the resting juice, and in 4 of the cases HCl was not present for a period of 1 hour. The disparity between the free HCl and total acidity ranged between 5 and 20 except in 1 case—Case No. 36—in which a disparity of 35 was noted. The emptying time varied between a minimum of $\frac{3}{4}$ hours and a maximum of 3 hours, the majority of cases retaining the gruel for $2\frac{1}{4}$ hours. Twenty-one of the 43 cases showed a better and higher secretion of HCl during the second $1\frac{1}{2}$-hour period than the first.

Bile was found at some stage of the digestion in 12 of the cases, but no blood was found in 1, and in none of the 43 cases was a secretory curve obtained to simulate in any part a pathological state.

In the one case in which the tongue was smooth and glazed—Case No. 6—a woman of 61 years, who looked pale and who secreted no HCl for 1 hour, the maximum HCl secretion was 20 c.c. N/10 NaOH, and the stomach emptied in 1¼ hours.

As all the figures regarding the volume, HCl, and total acid concentration are well within the normal limits, no further data of these 43 cases need be given.

TABLE IV.

High HCl Secretion.

Case No.	Age.	Sex.	Appetite.	Tongue.	Red Cells.	Hb %.	White Cells.	Resting Juice Volume.	Mucus.	Max. HCl.	Emptying Rate in Hrs.
								c.c.			
5	84	F	Good	Normal	—	—	—	25	Nil	55	1¾
24	66	M	„	„	4·9	88	8,000	40	„	70	1¼
37	79	M	„	„	—	—	—	15	„	90	2
40	68	F	„	„	5·0	80	4,800	10	„	60	1¾
43	71	F	„	„	4·7	78	7,400	15	„	56	3
45	72	M	„	„	4·7	74	6,800	20	„	60	2¼
50	78	M	„	„	4·8	68	9,000	25	„	54	3
52	60	F	„	„	4·8	80	7,200	12	„	60	2¼
55	91	F	„	„	4·9	82	9,800	25	—	50	3
56	81	M	„	„	5·2	90	10,000	30	„	65	2½
57	64	M	„	„	4·3	62	8,200	40	„	53	1½
62	63	M	„	„	4·8	78	9,600	30	„	95	3
95	75	M	„	„	5·5	90	8,500	15	„	52	2

D. *High Secretion of HCl.*

Thirteen cases showed a secretion of HCl, reaching above a value of 50 c.c. N/10 NaOH. The highest secretion of HCl recorded was equivalent to 95 c.c. N/10 NaOH or 0·35 of HCl. The appetite was noted as being good in all these cases, and in all the tongue was observed to be normal. No anaemia was apparent, and none complained of dysphagia. There was no history suggestive of previous digestive ill-health. The ages of this group varied between 61 and 91; 8 were males and 5 were females. The systolic B.P. varied between 140 mm. Hg and 280 mm. Hg systolic, and sclerosis of the vessels was observed in all of the cases to a varying degree.

The volume of the resting juice varied between 10 and 40 c.c., the average being 20 c.c. The odour was not abnormal in any of the cases, and in only 1, a woman of 91, was there any excess of mucus found. Eight of the 13 cases possessed no free HCl in their resting juice, and the maximum disparity between the HCl and total acid values observed was 50—in the resting juice of Case No. 57—but no offensive odour was noted. The rate of emptying varied between 1½ and 3 hours, the average being 2½ hours. Nine of the 13 cases showed a higher secretion in the second 1½-hour period than in the first.

Neither blood nor bile was observed in any of the secretions. In 1 only—Case 57—was there any degree of anaemia demonstrable, with a red cell count of 4·3 million and an Hb per cent. of 62.

Discussion of the Results.

The analysis of the 100 cases shows that the largest group comprises those cases falling within normal limits—43 per cent. But even in these cases a certain diminution in volumes of juice occurred, and the meal was frequently found unchanged in the withdrawn samples. A definite delay in secretion was observed in 23 of the 43 normal cases during the first 1-hour period. Many of

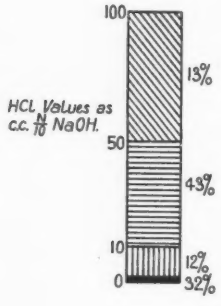

FIG. 1.

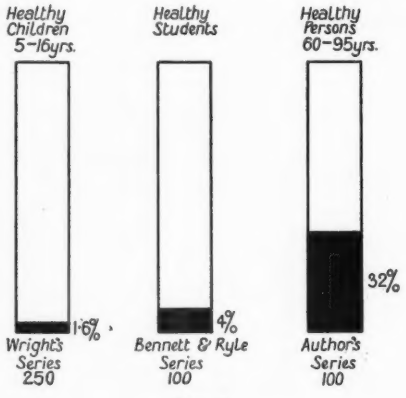

FIG. 2.

our cases were somewhat disturbed at having a gastric analysis, and the unnatural experience of having a tube in the stomach for the first time at their time of life undoubtedly played some part in the inhibition of the first hour. The percentage of 43 within normal range obtained by us contrasts with the 80 per cent. found by Bennett and Ryle in the healthy students, and indicates a progressive decline in function of the gastric glands. Figure 1 shows graphically the four groups of the series, in terms of HCl values as cc. N/10 NaOH.

In reviewing the series we shall attempt to bear in mind the following points—the frequency of achlorhydria at this time of life, the relationship of achlorhydria to carcinoma of the stomach and its importance from a diagnostic standpoint, and the relationship of achlorhydria to anaemia. From our series of 100, 32 showed no secretion of free HCl, as judged by the ordinary methods in routine use. This is a large proportion, and by its frequency minimizes the importance of this finding as a diagnostic help in establishing the presence or absence of carcinoma in a man over 60 years. Comparing the incidence of achlorhydria in our series to those obtained by investigators at other periods of life we obtain striking differences, and Figure 2 shows the definite increasing incidence with age.

By means of histamine it has been possible to distinguish between true and apparent achlorhydria, and from a possible percentage of 32 the true achlorhydria group were further differentiated into a number of 14. It can be taken as certain that the percentage of absolute achlorhydria in this series of 100 is not more than 14–16, since the group of 5, which was not fully investigated, would not yield on *a priori* grounds more than 2–3 true achlorhydrias.

A rough parallel between the volume of the juice and the acid response to histamine occurred—those in which a free secretion of juice followed the injection of histamine generally showed free acid present in the juice, while those in which no HCl was secreted after histamine showed little or no increase in the volume of the juice. It was also seen that all those cases where HCl appeared after histamine stimulation also showed definite amount of pepsin in the juice, and no case was encountered in which HCl was found without its accompanying pepsin. That the amount of pepsin and the concentration of acid bore little relation to each other was shown by many of the cases of that group of apparent achlorhydria (Fig. 1). For example, in Case 99, although the HCl content rose to a figure of 40 c.c. N/10 NaOH, and the volume to 15 c.c. after histamine, it is seen that the pepsin remained at a low figure of 16 units, while in Case 15, with the HCl at a value of 26 N/10 NaOH and the volume 10 c.c., the pepsin content was a figure of 512 units. Case 31, a man aged 67, showed a pepsin content of 1,020 units after histamine, with a free HCl of 40 c.c. N/10 NaOH; even the resting juice in this case, although containing no free HCl, had a peptic activity of 520 units. In three of this series which showed HCl after histamine the pepsin reached figures of over 500 units, i.e. that at least $\frac{1}{250}$ of a c.c. of gastric juice was able to digest the standard protein solution, and these three cases, like the others of the series, had previously shown achlorhydria by the ordinary method of analysis.

Turning now to that group of 14 which remained as achlorhydria after histamine (Table II), in none of these cases was the ferment found to be completely absent. The lowest figures were obtained in Cases 92 and 97—in the former digestion occurred up to a dilution of $\frac{1}{4}$ c.c. a peptic activity of 8 units, and in the latter up to a dilution of $\frac{1}{8}$ c.c., 16 units—and in both of these cases these figures were only obtained after histamine stimulation. In 4 cases the resting juice was found to contain no pepsin. Case 10 showed the highest content of ferments, and that was found in the specimen withdrawn 30 minutes after histamine, the sample possessing a peptic content of 512 units: unfortunately in this case the resting juice was not examined for pepsin. But a number of other cases in this series shows that histamine stimulates the production of pepsin as well as free acid secretion. Indeed, in this group pepsin secretion occurred quite independently of acid. As is seen in Case 28, while the resting juice contained no pepsin the sample withdrawn 15 minutes after histamine injection showed a pepsin content of 120 units, and that in spite of the absence of HCl secretion. These cases show, therefore, the independence of HCl and pepsin secretion, and that absence of titratable HCl does not mean

of necessity an absence of pepsin. The frequency with which this was found in the series points to the increased sensitivity of HCl secretion, and that it may possibly be the first ingredient to disappear from the gastric juice. In none of this series which showed true achlorhydria was pepsin found to be completely absent, and from this it must be concluded that a series of 100 persons over the age of 60 need not of necessity contain any cases of true achylia. This possibility of an earlier derangement to the acid-producing cells is a matter of some interest; although this has not been proven it seems to suggest that the HCl secretion is more vulnerable. If the failure of the stomach to secrete free HCl after histamine is taken as final and absolute evidence of inability to secrete acid, what the function of pepsin can be in this state of achlorhydria remains unknown. On the other hand it may be that the natural stimuli are more potent producers of acid than those used in gastric analysis. In view of the recent American work, especially that of W. B. Castle of Boston, on the necessity for a healthy gastric juice in preventing pernicious anaemia, and on the power of gastric mucous membrane to produce a remission in cases of pernicious anaemia, it may be that this unknown factor contained in gastric juice is a secretory product, which goes hand in hand with pepsin, for it is an established fact that the gastric juice of patients with pernicious anaemia contains no pepsin. Since Castle has shown that healthy gastric juice is able to act on beef muscle in neutral solution, and yet produce a product capable of inciting a remission in pernicious anaemia, it seems that the secretion of pepsin in these achlorhydrias may not be so unimportant as it first appears.

An inspection of the blood-counts in this series shows no case of marked anaemia, and far lower figures were anticipated, for many of the individuals with achlorhydria were unduly pale, and it was somewhat surprising to obtain such relatively normal figures. While only 1 of the 13 cases which showed an abundance of HCl secretion possessed a red cell count below 4·5 million, 7 of the 14 true achlorhydrias showed a blood-count below this level, and 5 of these 7 had red cell counts ranging between 3 and 4 million. While only 1 of the 13 cases with high HCl secretion showed a haemoglobin below 65 per cent., 5 of the anacidity group showed figures below 65 per cent. The lowest count was found in Case 42, a woman of 73, with a red cell count of 3·4 million and an Hb per cent. of 60. The colour index was found above 1 in only one case—Case 7—with a red cell count of 3·7 million and a Hb per cent. of 84. Of the 13 apparent achlorhydria cases, which secreted free HCl after histamime stimulation, a red cell count below 4 million was only found in 1, and the Hb per cent. below 60 in 3. In only 3 cases was there any material departure noted in the blood-films—Cases 42, 92, and 97 respectively. All 3 cases belong to that group which failed to secrete HCl after histamine, and all 3 possessed red cell counts between 3 and 4 million. The films of these 3 cases showed many red cells larger than normal, the most marked change being found in Case 42; the large forms were well filled with hæmoglobin and more oval than circular in outline. In Case 92 many rod-shaped erythrocytes were seen, polychromato-

philia was conspicuous by its absence, and in all other films no abnormal feature was noted, but in those showing a diminished Hb content central pallor of the erythrocytes was common.

From the above and the data tabulated herein it is seen that while the blood picture is not greatly changed from normal, such as is found occurs with greater frequency in those persons showing true achlorhydria than in those with apparent achlorhydria, and contrasts as a series with those possessing an abundant HCl secretion. It may be because a hundred more or less healthy persons have been chosen that the changes are not more definite, but sufficient differences are found to suggest a connexion between the blood picture and the character of the secretion. It is interesting to note that the two cases (92, 97) which showed the lowest pepsin content after histamine also showed red cell counts of 3·8 and 3·7 million, and with Case 42 showed definite changes in the size of the red cells. Case 18 is the exception in that, although the ferments stood at a low level and the patient also showed definite atrophic changes in the mucous membrane of the tongue, yet no anaemia was found; in fact, the red cells were 5·2 million and the Hb was 80 per cent.

In none of the cases was an anaemia found of such a character as to be classed as pernicious. But although complete achlorhydria was present in the cases showing some degree of anaemia, complete absence of pepsin was not demonstrated in them. It is here the difference appears to lie, for in the gastric secretion of a pernicious anaemia patient, even after histamine and even after complete return to health with liver therapy, there still remains an absolute achylia, and no pepsin can be found. In none of these cases was such an advanced functional deficiency discovered. It is therefore possible that these cases of anaemia are intermediate in type, and it is a matter of speculative interest whether, if these patients had developed the gastric change early in life and the change had become progressive, the departure from a normal blood picture to that of frank pernicious anaemia would have come about.

In none of the cases of anacidity examined in this series were there any symptoms or signs suggestive of a spinal cord involvement.

It was observed that in only one of the forty-three cases with normal secretion, and in none of those showing a high secretion of HCl, was the mucous membrane of the tongue found to be atrophic. Although a glazed tongue was found only in four cases of the true achlorhydria group, yet its occurrence was noted more frequently in this than in other groups, and emphasizes that the two findings may be found together—atrophy of the mucous membrane of the tongue and an abnormal or deficient gastric secretion.

At the commencement of this investigation it was thought advisable to make special record of the state of the peripheral arteries and of the blood-pressure, but it was found that the variations in pressure and degree of sclerosis of the peripheral arteries bore no apparent connexion with gastric function nor with the incidence of achlorhydria.

Summary.

1. Out of a series of 100 persons ranging between 60 and 95 years of age 43 showed a normal secretion of HCl, 13 showed a high secretion of HCl, 12 showed a diminished secretion of HCl, and 32 showed no free HCl secretion.

2. Small volumes of juice and an inhibition to secretion during the first 1–1½ hours were common findings in all.

3. Achlorhydria, by the use of histamine, could be divided again into as many apparent as true, thereby making the percentage of true achlorhydria to be 15 per cent. (approximately).

4. The ferment content of the gastric juices varied in the majority, and bore little relationship to HCl secretion.

5. In none of the cases of achlorhydria was pepsin found to be completely absent.

6. Histamine stimulated pepsin production in addition to HCl secretion.

7. Pepsin secretion occurred in the absence of demonstrable HCl secretion, but no case was encountered possessing free HCl without pepsin.

8. The secretion of HCl appears to be more susceptible to outside factors than that of pepsin, in that it is more easily inhibited or more quickly deranged.

9. Anaemia was more commonly found in those possessing a diminished gastric secretion than in those with an abundant secretion.

10. Anaemia, although slight in degree and indeterminate in type, was more common in those possessing a low ferment content of the gastric juice than in those with a high ferment content.

11. Atrophic changes of the mucous membrane of the tongue were found with more frequency in those cases showing a diminished secretion of gastric juice than in those with a normal secretion.

It is with pleasure that we record our acknowledgement to Dr. W. E. Turner, Medical Superintendent of the Park Royal Hospital, for his kind permission in granting us freedom to investigate all the cases herein referred to, and our grateful thanks to Prof. E. C. Dodds, M.V.O., for his constant encouragement and criticism.

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BUNDLE BRANCH BLOCK[1]

A CLINICAL AND HISTOLOGICAL STUDY[1]

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With Plates 1 to 3

WHILE of late years numerous series of records and case analyses have been published on this subject, in few instances has there been an attempt to trace histologically a causative lesion. In the present paper are given an analysis of forty-one cases of bundle branch block, various experimental and clinical observations on such cases as came under personal notice, and a report on an attempt to trace the lesion to the affected branch in two cases.

1. *Analysis of Cases.*

The cases selected number forty-one; of these thirty-two occurred in a total of some 4,000 consecutive cardiac cases examined electrocardiographically in the Royal Infirmary of Edinburgh, while nine occurred in the private practice of Professor W. T. Ritchie.

The selection was based on the electrocardiographic features, only such cases as conformed to the criteria of 'complete bundle branch block', as laid down by Carter (4), and confirmed by Lewis (18), and by Wenckebach and Winterberg (28), being included. In all the cases the initial ventricular deflection exceeds 0·1 second, constitutes one-third or more of the total complex, is of large amplitude and opposite sign in leads *I* and *III*, shows notching in one or more leads, and is followed in leads *I* and *III* by a well-marked *T* of opposite sign.

Age incidence. In the present series two cases occurred in the fourth, seven in the fifth, fifteen in the sixth, and nine in the seventh decades, while eight were over 70 years of age. Thus, as in other series, the great majority of the cases occurred in the degenerate period of life (8). These figures are shown graphically in Fig. 1, along with similar figures for various authors' series (Cowan and Bramwell (8), Hart (13), Herrick and Smith (14), Talley and Reed (25), and Willius (29)).

Sex incidence. Males number 31; females 10; the percentage of females is 24·4. This compares with other figures of 16 per cent. (8), 32 per cent. (25), 36

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per cent (13), and 42 per cent. (29). In all it is apparent that roughly two-thirds of the cases are males.

Incidence of right and left cases. Of the forty-one cases, only two were of left bundle branch block, an incidence of 4·8 per cent. Other published series give the percentage of left cases as 4 (8), 4·55 (4), 5·7 (29), 8 (13), 8·6 (14).

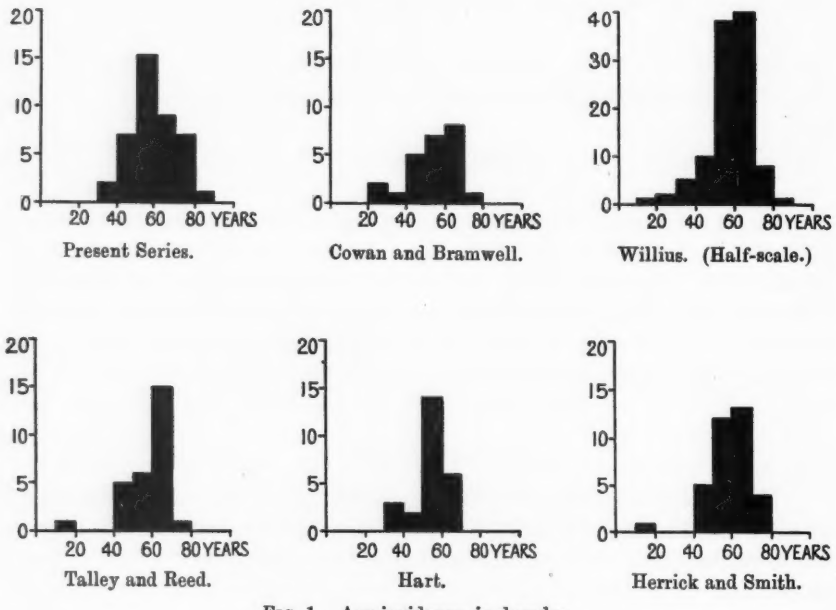

FIG. 1. Age incidence, in decades.

Relation to cardiac failure. Hart (13) states that 'these lesions have been seen only in cases of advanced heart disease'. Herrick and Smith (14) found that 48·5 per cent. of their cases had 'clinical manifestations of advanced heart disease'. All the 105 cases of Willius's series (29) showed dyspnoea on exertion; there was orthopnoea in 4 per cent. and congestive failure in 13 per cent., and the anginal syndrome occurred in 30 per cent. He states that 'it is interesting to note that most of the patients were ambulatory without great difficulty'.

In the present series, of the thirty-seven cases where clinical records are available, there was a pronounced degree of cardiac failure in practically all. In three there was orthopnoea, and in other twelve dyspnoea even at rest, and in most of the remainder there was breathlessness on exertion. Anginal pain was present in fifteen cases (40 per cent). Oedema was noted in twelve cases, in some being extreme.

Aetiological factors. The association with cardiovascular syphilis was less in this than in certain other series. In a recent paper, Bach (1) out of seventy-

eight cases of bundle branch block isolates a syphilitic group of seventeen cases, all with aortic incompetence and with a poor prognosis; he also notes four cases of right bundle branch block in 30 cases of aortic incompetence attending hospital in one year. Willius (29), on the other hand, gives 4 per cent. as the incidence of cardiovascular syphilis, and to this adds one case of rheumatic aortic incompetence. Out of twenty-two cases of bundle branch block, Carter (4) had eight associated with aortic valvular disease, 36·4 per cent.

In the present series only four cases showed aortic incompetence (9·5 per cent.), and a positive Wassermann reaction was obtained in four cases out of twenty-two where the test was made. In the remaining cases there were but two where syphilis was suspected. The incidence of syphilis is thus under eighteen per cent.

Rheumatism was also an uncommon precursor, there being a definite history of acute rheumatism in three cases only, while, in a few others, valvular lesions suggested its influence without evidence from the history.

Several of the cases in the series were found in association with toxic goitre; and for the case records of these I am indebted to Dr. John Eason. Though in these such factors as high blood-pressure were also active, the temptation is strong to regard the condition as dependent on the thyrotoxicosis, and strong corroborative evidence for this view is given below.

By far the most frequent type was that occurring in hearts undamaged by syphilis or rheumatism, in patients over middle age, often the subjects of hyperpiesis. The blood-pressure was recorded in thirty-three cases; and of these fifteen showed a systolic pressure of over 170 mm. Hg, seven being over 200 mm. In Herrick and Smith's series 66 per cent. had systolic pressures over 175. In Willius's series, of the various factors 'myocardial disease associated with hypertension occurred with greatest frequency' in 52 per cent. (29).

None of the present series occurred in young people the subjects of congenital heart disease, such as have been recorded elsewhere (25). An interesting case of the development of left bundle branch block in a case of defect of the interventricular septum and associated abnormalities was recently recorded by Baumgartner and Abbott (2).

Prognosis. Only a minority of the patients could be traced. Of fifteen, nine were dead after an average period of survival of 14·4 months, while six survived with an average of about 18 months. The mortality is therefore over 60 per cent., with an expectation of life of just over a year. This high mortality is due to the associated pathological changes, for, as Carter puts it, 'an organic lesion confined to one branch of the *a.-v.* bundle is hardly one which can be regarded as jeopardizing life'. A small series of seven cases, which did not present the full picture of bundle branch block, but were otherwise analogous in degree of failure, &c., showed a mortality rate of 100 per cent., with an average period of survival of nine months, a result which, with the reservations attendant on a small series, may be interpreted as confirming the opinion that the mortality is not dependent on the bundle branch block *per se*.

Associated electrocardiographic abnormalities. (*a*) Auricular fibrillation: This occurred ten times in the series, 23·8 per cent. This agrees closely with the 21 per cent. of Cowan and Bramwell. Willius, on the other hand, gives a figure of only 4 per cent.

(*b*) Auriculo-ventricular heart block. While lengthened *P–R* intervals were noted in several cases, complete *a.-v.* block occurred five times in the series, i.e. in 12 per cent.

(*c*) Extra-systoles. Carter states that, in most cases of bundle branch block, extra-systoles arise in the ventricle opposite to that in which the aberrant beat originates, and suggests that the lesion producing the defective conduction in a branch also provokes extra-systoles from it. In nine cases the origin of the extra-systoles has been studied, and no confirmation of Carter's statement has been found. It is suggested that the recording of extra-systoles is so much a matter of chance that no valid evidence can be drawn from their fortuitous appearance on routine examination.

II. *Clinical Observations.*

Diagnosis from physical signs. Since the appearance of Cowan and Bramwell's paper with its statement that diagnosis is possible only from the electrocardiogram (8), King has disputed this, and set forth various signs by means of which diagnosis of the condition 'is possible in most cases by the bedside' (15). The signs on which he lays stress are: (*a*) visible, and (b) palpable bifid apex thrust, and (*c*) feeble heart sounds, with a sound and an asynchronous murmur accompanying the two elements of the bifid apex thrust.

In a few of the present cases careful search was made for all of these signs. In one only was a bifid apex thrust noted, a sign which later disappeared without change in the characteristic electrocardiogram. In all, the heart sounds were faint; in one, inaudible. In four cases there was a reduplicated first sound at the apex; in two, an apical systolic murmur; and in one case, both a reduplicated first sound and a systolic murmur were heard. Of three cases presenting canter rhythm two lost the sign without electrocardiographic change; and of these two were typical cases of bundle branch block and the third was atypical.

Faint or muffled sounds and an apical systolic murmur each occurred independently in about half the cases of the whole series. These signs occurred together in less than one-sixth of the total. Reduplication of the first sound at the apex occurred in one quarter, and of the second sound at apex or base in one-third of the total.

Faint sounds or an apical systolic murmur are thus the commonest auscultatory signs, but they are not characteristic of bundle branch block. The signs of ventricular asynchronism to sight and touch are too rare to be of practical value, and even when they do occur are unstable. A reduplicated mitral or tricuspid first sound can be of little diagnostic value, for these are known not only to occur in cases other than bundle branch block but to disappear in cases while the block persists.

The conclusion, that diagnosis from physical signs is not feasible, is confirmed.

Response to digitalis and atropin. In two cases, doses of atropin sulphate were given (gr. 1/50 to gr. 1/30), sufficient to produce an acceleration of 20–30 beats per minute in the pulse. Serial records, taken at five-minute intervals during the period of action of the drug, revealed no detectable changes in the duration or form of the *QRS* complexes.

Digitalis is stated by Hart (13) to 'produce conspicuous changes in the graphic records', which appear at an early stage of digitalization, and are attributed by the author to the enhanced effect of this drug in pathological states. They consist in prolongation of the initial deflections, increase in amplitude and duration of *T*, and the production of extra-systoles from the ventricle on the side opposite the intact bundle branch.

In one case, a man of 62 received eight drachms of the tincture of digitalis within thirteen days, and records were obtained daily. From these no confirmation has been obtained of the claims of Hart. There was no special frequency of extra-systoles, nor was there any detectable change in the duration of the initial deflections or of the entire complexes, and the amplitude of *T* was not modified.

III. *Histological Results.*

References may be found in the literature to fifteen cases in which an attempt was made to find a lesion histologically in cases of bundle branch block. Lewis (18) in 1925 cited four cases in which a lesion had been demonstrated in the branch suspected from the electrocardiograms. To these positive findings must be added one case by Mahaim (19), one by Campbell (3), and one by Taussig (26). In the last the histological lesion involving the left branch was clearly demonstrated, but the electrocardiographic records are not convincing, the bundle defect only appearing in a record taken a few hours before death. Of the other eight cases previously investigated, four showed no lesion (Cohn and Lewis (7)), in two the evidence was doubtful, and two yielded lesions on the opposite side to that indicated by the electrocardiogram (Oppenheimer and Pardee (22)). This last paper is criticized by Mahaim (19), and little need be added to his comments.

Material from two cases was available for examination. As a preliminary, however, the septal portion of a normal heart from a child of eleven months was embedded and cut. Serial sections, of 10 μ thickness, were cut in the horizontal plane (long axis of the main stem of the bundle). Staining was by van Gieson's method, which was found, after trial of several others (e. g. Thiazin red), to be the most satisfactory. The bundle bifurcated in sections 350–420. Both branches were identified and followed without difficulty. The right branch passed downwards and from left to right through the septum, to take up a position less than a millimetre from the endocardium of the right ventricle, where it ran downwards, isolated in a loose connective tissue sheath, among the fibres of ventricular muscle. Some three millimetres below the

bifurcation, however, the right branch acquired a close relationship with a fasciculus of the muscle, in which it lost its identity in section 820.

The specialized tissue of the branches stains with van Gieson like that of the main stem, in a distinctively lighter tint than cardiac muscle, only in the first parts of their course. At lower levels the right branch does not stain differently from the myocardium in general, and cannot be identified except by continuity in serial sections. This difficulty was noted by Cohn and Lewis (7), who state that, wanting a distinctive histology, the continuity of the right branch in one case was lost. The tenuity of the right branch, and the fact that by this method the lower levels are cut in transverse section, add to the difficulty of identification.

The history and clinical findings of the cases subjected to histological investigation are as follow:

Case 1. A man, aged 73, was admitted to hospital on 7. v. 27, and died on 7. vi. 27. The history was of a complete breakdown in health of six weeks' duration, following on an influenzal attack. His speech had been noted to be peculiar for a year, and he had had breathlessness on exertion for two years. On examination there were well-marked signs of tabes dorsalis. The pulse was intermittent, its rate 70 per minute, and the vessel wall was thickened. Blood-pressure 150/90. Heart was not much enlarged; apex impulse feeble; all sounds pure but faint; and no reduplication of any sound. Two days before death the heart dilated considerably, but the sounds had not changed. Albuminuria was marked, and the liver was slightly enlarged. Death was due to an intercurrent bronchopneumonia. Post-mortem examination revealed also the lesions of tabes, cystitis, chronic pleurisy, and chronic interstitial nephritis.

In the electrocardiogram (Fig. 2) taken three weeks before death a sinus rhythm is present; the initial deflections in all three leads are of large amplitude and long duration (0·14–0·15 second); the main initial deflection is upward in lead *I* and downward in lead *III*, while *T* in lead *I* is negative, in lead *III* positive; and there is notching of the descending limb of R. The electrocardiographic features are typical of complete bundle branch block.

Case 2. A male, aged 53, was admitted to hospital on 27. iv. 27, and died on 14. v. 27. History of progressive disability from cardiac failure for seven years; latterly bedridden, with severe nocturnal dyspnoea, but without oedema. On examination pale, cyanosed and orthopnoeic. Pulse regular, 85 per minute, expansion small, and wall thickened. Blood-pressure 114/70. Heart enlarged to right and left; apex feeble and diffuse. Heart sounds faint; mitral first replaced by a soft systolic murmur, second reduplicated; rough aortic systolic murmur. Later, sounds became fainter and galloping in type, the mitral first as well as second being reduplicated. Other gross signs of cardiac failure were present—crepitations in lungs, albuminuria, jaundice, with enlargement of liver to three inches below costal margin. Blood Wassermann reaction, positive. Progress was steadily downhill, with great dilatation of the heart, irregularity of the pulse, Cheyne-Stokes breathing, pulsus alternans, and well-marked canter rhythm. Death occurred suddenly, the respirations being noted to cease before the pulse. *Post mortem.* There was marked dilatation of the whole heart. Diffuse subendocardial fibrosis was noted in both ventricles, most marked toward the interventricular wall; and on section the muscle showed further diffuse fibrosis throughout, but again most marked in the septum, and near the mitral valve. The coronary vessels showed considerable atheroma.

The electrocardiogram of this patient (Pl. 1, Fig. 3), taken eleven days before death, is hardly typical of complete bundle branch block, and the case is not

included in the analysis above. Sinus rhythm is present, with a *P–R* interval of 0·24 second. By lead *I* the initial deflections are of moderate amplitude (8 mm,), positive, of long duration (0·17 second), and markedly splintered; and *T* is of low voltage, and positive. By leads *II* and *III* the initial deflections are of large amplitude, long duration (0·15–0·17 second), and negative sign, while notching is prominent. *T* in these leads is large and positive.

In Case 1 the bifurcation of the main stem was found to occur in sections 400–50. The right branch was followed through a further 200 sections, but in sections 620–30 it became very small. In section 630 it persists doubtfully as a fine strand cut in transverse section, with several similar strands grouped around it. To this level it had been running more or less in the plane of the sections, but in section 630 it had turned downwards through a right angle, and immediately split up into numerous branches. This had occurred certainly not more than 3 mm. from the bifurcation, when the left branch was still a well-defined, widely-spread, subendocardial structure. No lesion was seen in the left branch. Prior to its division, the right branch showed in its substance several vessels, much as in the normal main stem immediately above its division. In the right branch, at the same level as the vessels, were one or two ill-defined patches of cellular infiltration (Pl. 1, Fig. 4). In this case there was little evidence of generalized myocardial fibrosis.

In Case 2, each of the numerous portions of heart tissue examined showed chronic interstitial myocarditis. This was extreme in degree, but did not affect the region of the bundle branches in any selective way. No actual patch of fibrosis was seen in the bundle or its branches, though other lesions were found. The bundle bifurcated in sections 270–300, and the right branch was followed down, cut in transverse section, for 330 sections. In section 640 the right branch changed direction, and in section 750 it ran in the plane of the section. In section 770 it was seen as a wisp of tissue, a fine strand running deeply into the main muscle mass for 6 mm. (Pl. 2, Fig. 6). The distal (antero-inferior) end of this strand was soon lost among the muscle fasciculi, and after section 790 further tracing was impossible. There were numerous dense foci of round-celled infiltration scattered thickly throughout the heart tissue examined. They occurred in the auricular and nodal regions, in the septum, and in the ventricular muscle, complicating the picture of diffuse fibrosis referred to above. In two instances they appeared to implicate the conducting tracts. In one a dense focus was seen immediately in front of the main stem at a high level (Pl. 1, Fig. 5). In the other there was a similar focus, but smaller, involving the right branch in section 784, where the conducting strand is only two or three muscle fibres wide (Pl. 2, Fig. 7). These foci are dense aggregations of mononuclear cells, distinctly perivascular in distribution, and suggest a luetic origin. The Wassermann reaction in this case was strongly positive. It is noteworthy that the *P–R* interval in this case was 0·24 second. No lesion was detected in the main stem apart from the focus, to which reference has been made.

The usual anatomical description states that the right branch remains as

a single undivided strand till it reaches the anterior papillary muscle of the right ventricle (21). In one of the present cases it divided at a high level; and in both the others it lost its identity at a high level, findings which support Walmsley's (27) statement, 'that in some instances the right limb assumes the characters of the normal myocardium soon after it has left the main stem . . . or that there is a very early scattering of the fibres which are grouped together to form the limb'. That three successive cases should show this is probably fortuitous.

IV. *Incomplete Bundle Branch Block.*

Certain writers group as 'incomplete bundle branch block' all cases showing prolonged or deformed ventricular complexes of supra-ventricular origin exhibiting some, but not all, of those features laid down by Carter, Lewis, and others as typical of complete bundle branch block.

Thus Willius (30) groups as incomplete all cases which show the majority of the features of the complete condition but lack one or two essentials, e.g. notched biphasic complexes, with long *QRS* and oppositely directed *T*, but of low amplitude in one or other lead; or curves typical of complete bundle branch block in all but the direction of the initial deflexions in leads *I* or *III*; or with *T* in one lead atypical. In the large number of tracings reproduced in his work there are many (loc. cit., Figs. 159, 161, 164, 165, 166, 167, 169, 170, 171) which offer no appreciable divergence from those figured as typical of complete bundle branch block. He admits that 'the interpretation of these may vary according to the personal equation'. Again, his statement that he has never seen a case of complete bundle branch block as a temporary or transient disorder is invalidated by the curves he figures of transient cases (loc. cit., Fig. 175), which fulfil all the criteria of the complete condition as defined by Carter (4).

The term incomplete is generally used on the supposition that interruption of part of the conducting tract to the ventricle has taken place at a level below the division of the bundle branch—intraventricular or arborization block—a supposition for which no experimental support is forthcoming. The curves shown as incomplete bundle branch block are in many cases those of ventricular hypertrophies, and again and again in the present study curves of that nature have been considered and rejected. The spread of the excitation wave in a heart with gross increase of the muscle mass in one or other chamber is abnormal, and betrays itself by prolongation of the *QRS*, and modification of *T*, highly reminiscent of the curves of bundle branch block.

The term incomplete bundle branch block is used in another sense by Stenstrom (24), who contrasts delayed conduction and complete obstruction in the main stem, and like conditions in its main branches. Signs of bundle branch block may appear from delay in conduction, which may be of slight degree and temporary in nature. If a supraventricular impulse is delayed in its descent of the *a.-v.* bundle, the latitude allowed, before a ventricular beat

drops out, is considerable, and the *P–R* interval may increase from the normal 0·15 up to 0·5 second (Lewis). But a very slight delay in the transmission through one branch of the bundle is equivalent in result to a complete obstruction to its passage; for such a slight delay, of the order of 0·2 second, will suffice to render the arrival of the impulse at its ventricle later than that of the impulse which has travelled *via* the intact branch and the ventricular musculature of the other side. Such a delayed impulse, though not blocked in the sense of being completely obstructed, arrives to find its ventricle in systole, and so is ineffective. The electrocardiogram in such a case is indistinguishable from complete bundle branch block, as defined by Carter, or as understood by Willius.

Such a condition as Stenstrom postulates receives strong support from his published tracings. In one case, apparently of complete bundle branch block, slowing of the heart-rate by caroto-vagal pressure resulted in the ventricular complexes becoming normal. In another case, where alternate complexes were normal and aberrant, the aberrant complexes disappeared on slowing the heart-rate by caroto-vagal pressure, and became persistent on raising the heart-rate by exercise. In both the relation of the conductivity of the bundle branch to the length of the preceding resting cycle is well seen.

Similar cases have been recorded elsewhere. Leinbach and White have recorded two almost exactly comparable cases, in one of which a patient at rest had normal complexes, but with the tachycardia of exercise he developed temporary signs of bundle branch block, and in the other a patient showed alternate complexes of right bundle branch block and normal mechanism before the branch block became permanent (16). Again, there are the cases of Stecher of transient defects of branch conduction in diphtheria (23).

The experimental production of the condition is recorded by Lewis (18) when, during the recovery of the right branch after clamping, all grades of block between complete obstruction and normal conduction were recorded. The conception of delay in conduction in the main branches of the bundle has also been formed by Wilson and Hermann (31) from their experimental work.

In the present series several cases are worthy of consideration along these lines. I shall make no more than passing reference to the numerous cases of incomplete bundle branch block, as conventionally understood, which were encountered and excluded from this analysis. In many the curves, which fell short of the complete syndrome in one or two respects, fitted exactly into the class of ventricular preponderances, in which prolongation of *QRS*, opposite sign of initial deflexions in leads *I* and *III* and modification of *T* all occur.

In other cases curves show analogies with Stenstrom's cases. For example, in a record from a case in this series, figured lately by Gilchrist and Ritchie in another connexion (11, Fig. iii) the features of bundle branch block are well marked, the initial deflexions in lead *I* are only of moderate amplitude however (9 mm.), and the *QRS* of lead *III* is biphasic. After extra-systoles the records

by leads *II* and *III* show reduction of the duration of the *QRS* of the returning cycles from 0·14 to 0·08 second; in both leads the whole *QRST* complex is shorter by 0·03 second than the others in those leads; and in lead *III* the *T* of the returning complex is of opposite sign to the remainder, and the whole complex is almost normal. A year later this patient showed electrocardiograms in conformity with all Carter's criteria (Pl. 2, Fig. 8), and curves obtained two years after the original record are typical of complete branch block.

The interpretation seems to be that the original curves resulted from a delayed conduction of the impulse down the right branch of the bundle, so slight as not completely to nullify its effect on the ventricle, giving rise to aberrant complexes therefore, but not quite typical of complete bundle branch block. The lengthened resting period afforded by the occurrence of a ventricular extra-systole was then sufficient to allow of recovery in the function of the bundle branch, and the succeeding impulse was transmitted in normal time, but the branch reverted to its state of impaired function and delayed conduction in the following beats, which occurred after normally short resting cycles. This condition has persisted, and has probably gone on to organic interruption of the branch; the later curves are typical of complete bundle branch block; and extra-systoles now produce no effect on the succeeding complex.

A second case that illustrates the transient nature of the block in certain of these cases is that of a woman aged 52 years, the subject of toxic goitre, for details of whose case I am indebted to Dr. John Eason. The original records showed auricular fibrillation and well-marked right bundle branch block, with, in certain records, a variation in the form and duration of the *QRS* complexes that suggests variations in the function of the two branches of the bundle. Subtotal thyroidectomy had been performed previously (Fig. 11). A month after a second operation at which further portions of the gland were removed the normal cardiac rhythm was restored, but there was still evidence of branch block. Some three weeks later, with the heart-rate as low as 90 per minute, her records again show normal rhythm, but now without evidence of defective conduction through the bundle branch (Pl. 3, Fig. 12). Four days later her heart-rate rose to 120 per minute, and there was well-marked bundle branch block of the complete type, with persistence of normal rhythm (Pl. 3, Fig. 13). Her further progress was steadily downhill, with consistently rapid heart action, till her death some six weeks later. The disappearance of the fibrillation after thyroidectomy is ascribed to removal of the toxic cause. We may attribute that of the bundle branch block to a similar cause plus reduction in the heart-rate and consequent increased rest for the structures whose functions are impaired.

A similar case of disappearance of a branch block is that figured by Cowan and Ritchie (9), and is included in the present series. In this case the signs of block were present at the height of an attack of severe cardiac failure with anasarca and jaundice, in a patient with mitral stenosis (Pl. 2, Fig. 9). The block disappeared some weeks later, on recovery from the severe failure (Pl. 2, Fig. 10). By some, block has been associated with jaundice (8), but, though

admitting this possibility, we may note its association with malnutrition of the tissues, and with tachycardia, for in the records with signs of block the heart-rate is 105, and in the later records it is but 75.

These cases of transient or inconstant block afford examples of the condition which can hardly be due to organic changes in the bundle branches. Their temporary nature precludes destruction of the conducting tract. They are analogous to the condition of *a.-v.* block induced by digitalis, or occurring in the course of certain fevers (diphtheria, rheumatism), where lesions in the bundle, though such have been detected, are not constantly present.

A record of some interest is that from a case with well-marked signs of complete bundle branch block and auricular fibrillation, where an isolated ventricular complex shows marked divergence from the aberrant form (Pl. 3, Fig. 14). In this complex the duration of *QRS* is 0·12 as against 0·14 second in the remainder; the deep *S* with slurred apex and positive prominent *T* are replaced by high *R*, moderate *S* without slurring, and inverted *T*; and the whole complex lasts 0·35 as against 0·385 second. It is evident that conduction has here occurred down the right branch, and this in a case presenting all the features of complete bundle branch block of the right side.

It is urged that the term incomplete or partial bundle branch block be not applied to cases showing an imperfect electrocardiographic picture of that condition, but be reserved for cases showing analogy to incomplete heart block, namely, delay in, not necessarily failure of, conduction along a branch.

Attention is drawn further to the occurrence of cases in which the electrocardiographic picture of bundle branch block is inconstant or transient, denoting that the failure of conduction may be a disturbance of cellular function without irreparable damage to the tract, and without lesions recognizable histologically. As examples of causal agents of such a condition there may be cited the toxaemia of goitre or of pronounced cardiac failure, or the ischaemia of coronary occlusion. Doubtless the progressive nature of the last produces, in most cases, definite fibrotic involvement of the bundle branch, should its artery of supply be attacked, but a good example of bundle branch block as a *transient* incident in coronary disease is figured by Levine and Brown (17, case 55, Fig. 9).

The suggestive frequency of bundle branch block in hearts the seats of a slow generalized fibrosis of ischaemic origin, and the realization that it is frequently a consequence of vascular disease, render it probable that in many cases there is an early stage of ischaemia of the bundle branch with consequent impaired function, preceding the later fibrotic replacement that follows on prolonged anaemia. It is in cases at the earlier stage, and in those of 'toxic' origin, that incomplete bundle branch block is likely to occur. The conception of delay, constant or varying from beat to beat, in the descent of the impulse through one or both branches of the bundle, with consequent combination of levo- and dextro-cardiograms in varying time relations, and production of initial ventricular complexes of corresponding variety, yields a plausible explanation for such variability in these complexes as is clinically familiar. Such

an explanation accords with both experimental results (31) and theoretical considerations, and the use of the term incomplete block in this sense, sanctioned by analogy, is preferable to its application to an incomplete electrocardiographic picture, or to lesions of the ramifications of the bundle branches, whose occurrence and production experimentally are still matters of debate.

V. *Summary and Conclusions.*

1. Forty-one cases of bundle branch block are recorded, with clinical findings. Correlation with other published series as regards age and sex incidence and aetiology, has been carried out.

2. The diagnosis of the condition by means of physical signs alone has been investigated, and the conclusion confirmed that this is not feasible.

3. The influences of atropin and digitalis on the degree of block have been investigated in certain cases. No demonstrable change affecting the ventricular complexes was produced by therapeutic doses.

4. The right branch of the bundle has been traced by serial sections in two cases which during life showed the features of right bundle branch block. In both, and in one child's heart cut as a control, the right branch was found to split up or lose its identity at a higher level than was expected from anatomical teaching. In one case, in addition to widespread fibrosis of the myocardium which did not involve the bundle or its branches, foci of round-celled infiltration were demonstrated in the main stem and in the right branch. From their nature, and from the known syphilitic element in the case, these foci are thought to be possibly of a specific origin.

5. The question of 'incomplete bundle branch block' has been considered, and it is urged that this term be not applied to cases yielding an incomplete electrocardiographic picture of bundle branch block, but solely to cases which show analogy to incomplete block of the main stem, i.e., delayed conduction. Several cases of this type are described.

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DESCRIPTION OF PLATES.

FIG. 2. *Case 1.* Electrocardiograms. Time marker in this and similar records, 28·57 per second.

FIG. 3. *Case 2.* Electrocardiograms.

FIG. 4. *Case 1.* Microphotograph, × 60, section 615. The right branch, indicated by black lines, is seen in a loose sheath, well defined, with one large and numerous small vessels in its substance.

FIG. 5. *Case 2.* Microphotograph, × 1,000, section 199. Shows the perivascular focus of round cells in the main stem of the bundle.

FIG. 6. *Case 2.* Microphotograph, × 16, section 770. The right branch is seen immediately above the level at which it is lost: a fine strand indicated by arrows, running in the plane of the section.

FIG. 7. *Case 2.* Microphotograph, × 140, section 784. Shows a small focus of round cells in the right branch.

FIG. 8. Electrocardiograms, F. S., 26.ix.28. Showing the persistence of bundle branch block one year after the original records.

FIG. 9. Electrocardiogram, W. T., 12.ii.14. Well-marked right bundle branch block.

FIG. 10. Electrocardiogram, W. T., 6.iv.14. Record from same case seven weeks later: no signs of bundle branch defect.

FIG. 11. Electrocardiogram, J. W., 16.viii.27. Shows right bundle branch block, auricular fibrillation, and several anomalous complexes in leads *I* and *II*.

FIG. 12. Electrocardiogram, J. W., 18.x.27. Normal rhythm without bundle defect: heart rate approximately 90 per minute.

FIG. 13. Electrocardiogram, J. W., 22 x.27. Persistence of normal rhythm, with return of signs of bundle branch defect: heart rate approximately 120 per minute.

FIG. 14. Electrocardiogram, J. M. W., 11.v.22. Shows auricular fibrillation, with signs of right bundle branch block. One anomalous complex occurs in lead *III*. See text.

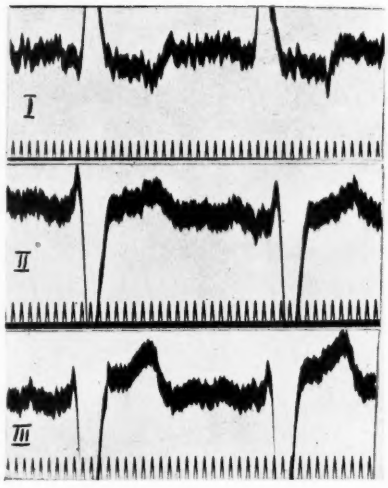

FIG. 2

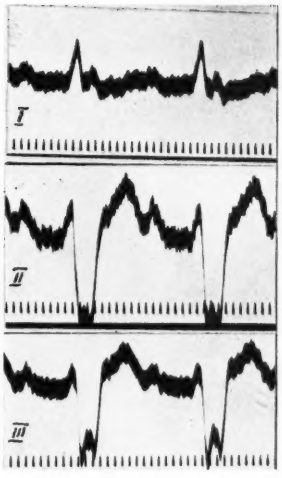

FIG. 3

FIG. 4

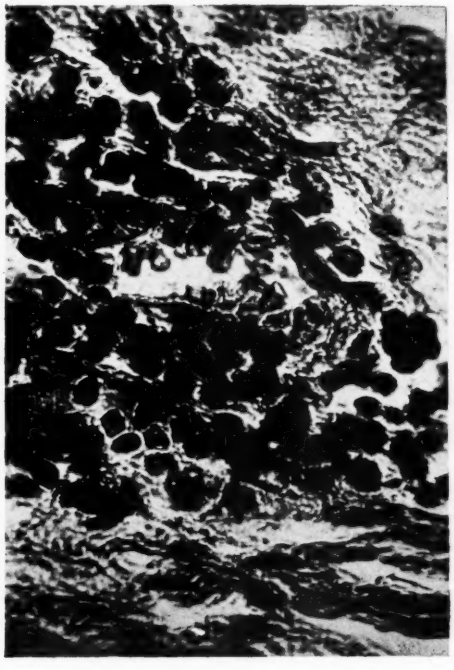

FIG. 5

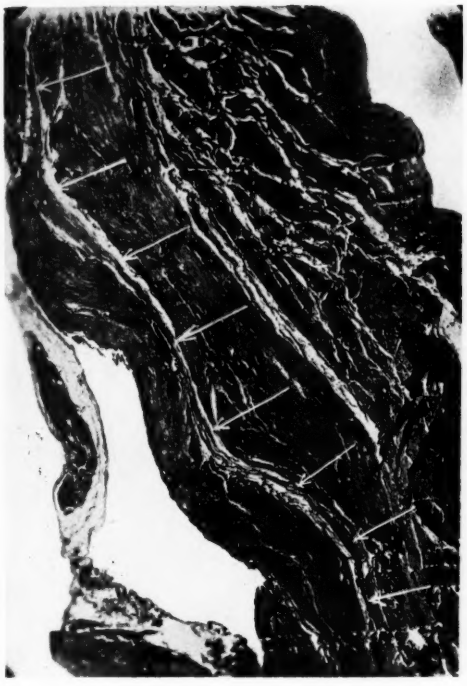

FIG. 6

FIG. 7

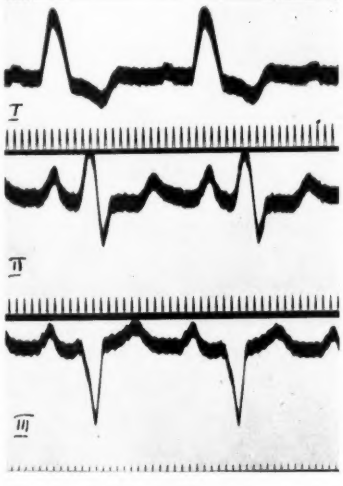

FIG. 8

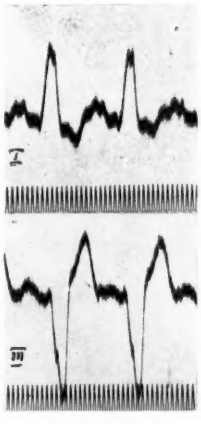

FIG. 9

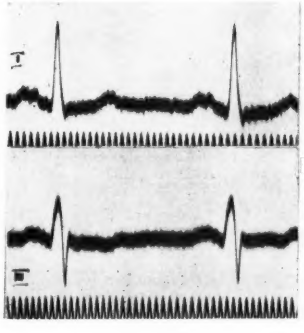

FIG. 10

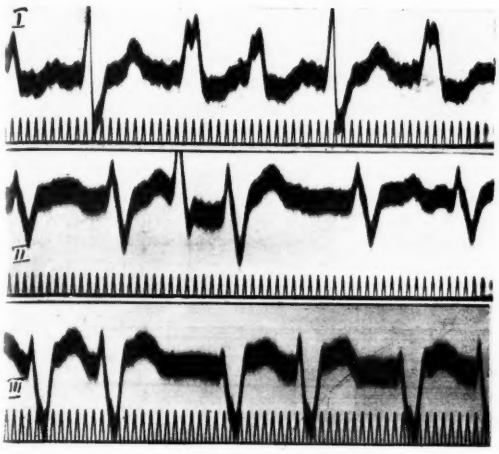

FIG. 11

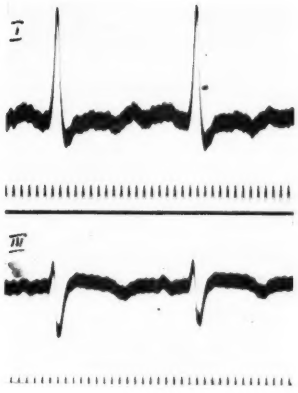

FIG. 12

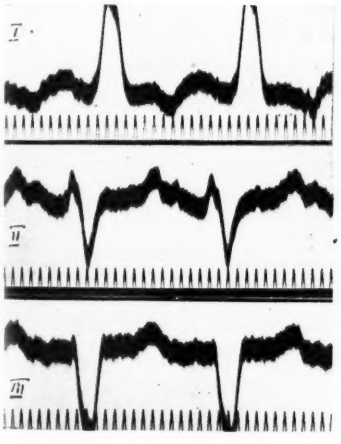

FIG. 13

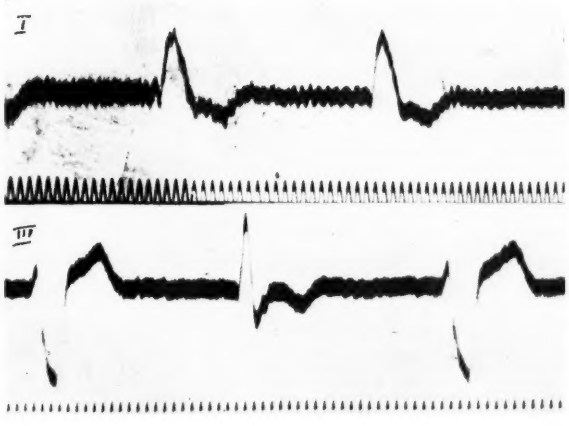

FIG. 14

616.233–006.465

A CLINICAL STUDY OF BRONCHIAL CARCINOMA[1]

By JAMES MAXWELL and W. A. NICHOLSON

This paper presents the results of a study of the clinical notes of a series of 100 cases of primary bronchial carcinoma in which the diagnosis was confirmed by post-mortem examination, and in which, therefore, we have been able to correlate the clinical with the pathological observations. At the outset we propose briefly to recapitulate a few of the main facts which have been brought out of recent years concerning the incidence and pathology of the condition.

Incidence.

It is becoming generally accepted that primary bronchial carcinoma is more frequently met with nowadays, both in clinical practice and in the post-mortem room. This increase is no doubt partly explained on the ground of improvement in clinical and pathological diagnosis. There has also been an alteration in our conception of the pathological nature of many of the tumours under discussion, although this does not affect the value of statistics which embrace the incidence of all varieties of primary malignant intrathoracic tumour, and the figures published by the majority of observers are classified in this comprehensive manner. We would refer particularly to the series of cases published by Duguid (5), Staehelin (18), Kikuth (10), and Simpson (17) as evidence that there has been an actual increase in the incidence of this type of disease in recent years, after making due allowance for the operation of all the possible factors which might influence the frequency with which these tumours are discovered, and recently Weller (19), and Rosahn (14) have reported a similar increase from America.

With this conclusion we are in complete agreement. In a recent paper (12) we published the results of a study of the annual incidence of primary malignant intrathoracic tumour in the post-mortem department of St. Bartholomew's Hospital from 1867 to the end of 1928. During this period there were altogether 204 cases, and analysis showed that, although the total number for any single year was small, never exceeding twelve cases, yet since the year 1919 there has been a very distinct increase in the annual case incidence.

We are indebted to the editors of the St. Bartholomew's Hospital Reports for permission to reproduce the table on page 30 a glance at which makes this increase clear. The figures for the years 1867 and 1869 are incomplete and they

[1] Received June 5, 1930.

are counted as one year for the purpose of the Table. Prior to 1884, the surgical records are not available, but it may be assumed that this deficiency has not caused any appreciable loss of intrathoracic tumours. It has, however, considerably influenced the figures for total post-mortem examinations and malignant growths, so that the percentage figures of this period are not comparable with those of later years. It can be seen, however, that there was a definite increase in the number of primary malignant intrathoracic tumours between the years 1896 and 1913, corresponding with a period of increase in the number of post-mortem examinations; analysis of the annual case incidence showed that

TABLE I

Period.	Total intra-thoracic growths.	Total post-mortems.	Percentage of post-mortems.	Total malignant growths.	Percentage of malignant growths.
1924–1928	45	1851	2·43	318	14·15
1919–1923	20	1992	1·00	296	6·76
1914–1918	11	2020	0·54	252	4·37
1909–1913	16	2665	0·60	329	4·86
1904–1908	23	2746	0·84	321	7·17
1899–1903	16	2557	0·63	350	4·57
1894–1898	25	2614	0·96	319	7·83
1889–1893	9	2540	0·35	269	3·35
1884–1888	10	2484	0·40	256	3·91
1879–1883	11	1362	0·81	130	8·46
1874–1878	9	1241	0·73	101	8·91
1867–1873	9	1155	0·78	80	11·25

The period 1867–1883 consists of figures from the Medical Post-mortem Register only.

the period of increase actually extended from 1896 to 1909, thus excluding the possibility that the disturbances of the war period had caused an artificial falling off in the number of cases. Examination of the annual figures for the last decade showed that the present period of increase commenced in 1920 and that thenceforward, with the exception of 1922, the annual case incidence has been greatly in excess of the average for the whole period, though the total number of post-mortem examinations has been appreciably less. Reference to the table also shows that the total number of malignant growths has been remarkably steady, so that the thorax is assuming increasing importance as a primary site of malignant disease; it is a most striking fact that during the last five-year period no less than one-seventh of the malignant tumours in the post-mortem room at St. Bartholomew's Hospital took their origin within the thoracic cavity.

Pathology.

Our conception of the pathology of this whole group of tumours has been considerably altered of recent years, as a result of closer histological study of the various types of tumour commonly found. It has long been realized that two main histological types of primary new growth may occur within the thoracic cavity. The less common but more easily explicable tumour is an obvious carcinoma, columnar, squamous, or spheroidal-celled; the majority,

however, consist of small oval-celled tumours which for many years were regarded as sarcomata, arising presumbly from some mediastinal structure and secondarily infiltrating the hilum of the lung. In 1926, however, Barnard (3) published a classical paper in which he brought forward convincing arguments in support of the view that these small-celled tumours are in reality also carcinomata and essentially similar in nature to the more obvious varieties of bronchial carcinoma. Subsequent papers have served to confirm this view, and further evidence in support has been brought forward by Shennan (16), Schuster (15), and Simpson (17). In a paper recently published by one of the present writers (11) a series of 184 cases of bronchial carcinoma is discussed in detail, and this view is accepted, evidence being brought forward to show that the small-celled tumours are in reality basal-celled carcinomata.

The separation of the tumours into their various types is effected by a study of their site of origin and their mode of infiltration, and it will be readily seen that there are four main possibilities.

The first and least common type is a local tumour which arises in the mucous membrane of a main bronchus and remains localized, either projecting into the lumen or forming a spherical mass surrounding the bronchus. In the second type the tumour invades and may replace the lung tissue; in the third the mediastinum alone is directly infiltrated by the growth; while in the fourth and commonest type there is a combined infiltration of lung and mediastinum. In view of the full descriptions of the pathological features of these tumours, to which reference has already been made, we do not propose further to discuss this aspect of the subject.

Clinical Features of Primary Bronchial Carcinoma.

The present series consists of 100 cases *selected* from the clinical records of St. Bartholomew's and the Royal Chest Hospital from 1912 to the beginning of the present year, all of which were verified *post mortem*. Not all of the possible cases have been included in the series, as occasionally important features were not noted, or the patient died within such a short time of admission to hospital that no adequate clinical history could be obtained. In each case the clinical notes and the post-mortem register have been consulted and the sections have been examined, so that the nature of the lesion has been verified in every instance, and the diagnosis is not in doubt. Histologically, forty-seven were typical carcinomata and fifty-three were basal-celled tumours. Ninety-four of the cases are included in the paper previously quoted (11), the remaining six having been added since that paper was published; seventeen of the cases had been under our personal observation during life.

Aetiology.

Sex. In this series eighty-three of the patients were males and seventeen females, a sex ratio of more than four males to each female. This preponderance

of males is rather greater than that which we found in our previously reported and more extensive series, which included most of the cases at present under consideration and in which there were 150 males and fifty-four females, but the difference is not of great significance. The majority of observers have found a preponderance of males, the ratio usually being between three and four males to each female. It is interesting to note that as long ago as 1897 West (20) found a sex ratio of three males to one female, a fact which suggests that, whatever the cause of the increase which has occurred, it is one which affects both sexes equally.

The *age* period of the disease is very extensive, the youngest in this series being 16 and the oldest 80 years of age. There is a great concentration of cases in the period of middle age, between the ages of 40 and 60, although the disease is by no means uncommon in younger subjects.

The actual age incidence was as follows:

Under 20 years	. . . .	3 cases
20–29	,, ...	7 ,,
30–39	,, ...	13 ,,
40–49	,, ...	31 ,,
50–59	,, ...	33 ,,
60–69	,, ...	11 ,,
70–79	,, ...	1 case
80–90	,, ...	1 ,,

Occupation. It was shown by Duguid (5) that in Manchester intrathoracic malignant disease occurred equally amongst indoor and outdoor workers. Taking into account, however, the fact that roughly 75 per cent. of the adult population in that part of the country are engaged in indoor occupations, he concluded that this type of disease is more likely to affect those whose occupations are mainly in the open air, the inference being that the inhalation over a prolonged period of some atmospheric impurity may play some part in the causation of the disease.

In the present series of London cases sixty-six were engaged in indoor and thirty-four in outdoor occupations. It must be remembered that a hospital in a large city draws its patients from a considerable part of the surrounding country, and the proportion of indoor to outdoor workers will vary with the proportion of city to country dwellers admitted. Also, we cannot be sure as to the length of time for which the occupation stated in the clinical notes had been followed, and we have to accept these statements at their face value; changes in occupation, recent or old, are not as a rule reflected in the notes, so that the classification is open to a very serious fallacy. Again, in many cases it is not easy to generalize as to the precise nature of some occupations on the lines of this classification, and such cases weaken the value of these figures. After careful consideration we have reached the conclusion that from our own figures, at least, there is no evidence to suggest that the outdoor worker is more liable to contract a bronchial carcinoma than his indoor colleague, and that the assumption of some atmospheric impurity to explain the increase in incidence of the condition is not justified by the evidence.

It must also be remembered that nearly the whole population spends so

much of their leisure time nowadays in the open air that such possible aetiological factors as tar and road dust and fumes of oil and petrol are likely to be of almost equal importance in all cases irrespective of their occupation.

With regard to specific occupations, there was none which occurred with marked frequency in this series, nor *post mortem* was any occupational lesion found which might have been held to account, even in part, for the presence of the growth.

Indeed, the only occupation which can at present be definitely held to play any part in the production of bronchial cancer is the mining of certain metals in Saxony. Of these metals, cobalt is the most important, and Arnstein (1) has reported that nearly one-third of the miners in the Schneeberg district admitted to hospital in the years 1907–1911 were admitted with a diagnosis of pulmonary cancer. Simpson quotes more recent figures for the same district, showing that the incidence of this condition still remains high, although the explanation of this phenomenon is not clear.

Previous health. There was a history of some previous chest disease in no less than forty-two of the cases. The commonest antecedent condition was chronic bronchitis, which occurred in the past history twenty-one times, although when it is remembered that the great majority of the cases occurred at an age period when this condition is exceedingly common, the fact is deprived of any great significance.

The other conditions noted were:

Pneumonia and broncho-pneumonia	7
Influenza	7
Pleurisy	5
Pleurisy with effusion	1
Gassed in the war	4
Phthisis	3
Injury to chest	1

There was therefore evidence of some previous acute inflammatory process involving the lung or pleura, or both, in nineteen of the cases. Attention has been drawn (11) to the fact that *post mortem* there are frequently dense pleural adhesions on the side affected by the carcinoma. These adhesions frequently appear to be of much longer duration than the growth itself, and a tentative suggestion has been made that pleural adhesions, by limiting the ventilation on one side, may lead to a concentration of an irritant substance in the bronchus on the affected side and thus predispose to the development of a malignant growth. The frequent occurrence of these old adhesions is explained, in part at least, by the occurrence of these acute respiratory diseases in the past history. In four of the cases there was a note of excessive tobacco smoking in the past history, although the information on this point in the other cases was very incomplete; there was certainly no suggestion from the notes that the inhalation of tobacco smoke plays any part in the production of the condition.

Three other aetiological factors have to be considered here. It has been considered by Berblinger (4), although there is no convincing evidence in support of the contention, that the present increased incidence of bronchial

carcinoma may be a sequel to the influenza pandemic of 1918–19, and in our own series the recent increase appears to have commenced in 1920. The Manchester figures (5), however, do not appear to have been affected in any way by the outbreak, and Staehelin (18) found that the increase at Basle commenced before the epidemic of 1918 occurred. In the present series, influenza was only noted in the previous history in seven cases, and in three of these the attack had occurred more than twenty years previously. It would appear from this that influenza need not be seriously considered as a factor in the causation of the condition. Similarly, there was a history of gassing in the war in only four of the cases, and we could find no suggestion of an aetiological relationship in this fact. The views of Ewing (7) have frequently been quoted in support of an alleged connexion between pulmonary tuberculosis and cancer. We have not been able to confirm this suggestion in our own series of cases, and our experience is confirmed by that of Schuster (15), Morris and Landis (13), Kikuth (10), and many others. The other diseases which were noted were such as might have occurred in any series of cases and need not be particularized. In one case the patient was stated to have received a severe blow on the chest one year before the development of symptoms. Aufrecht (2) considered severe trauma to be an important immediate cause of pulmonary carcinoma, and similar cases have been recorded by Georgi (8) and others, yet such records are so few comparatively that a single severe injury cannot be accepted as important in determining the onset of pulmonary carcinoma.

Total duration of symptoms. It is obviously impossible to arrive at any accurate conclusion as to the date of origin of the disease. Accordingly, we have been obliged to calculate the duration of the disease from the time of development of the earliest definite symptom. In some cases minor symptoms had been noticed for months or even years before this date, yet we did not feel justified in including such indefinite symptoms in our calculation of the duration of the disease, and consequently the total duration of the symptoms has probably been underestimated. The following table shows the total length of life after the onset of the first definite symptom:

Over 4 years	1 case
3–4 „	5 cases
2–3 „	7 „
1½–2 „	4 „
1–1½ „	9 „
½–1 „	38 „
3–6 months	28 „
Less than 3 months	8 „

The longest duration was five years and the shortest one week in a patient who had been entirely free from symptoms until the onset of a large and fatal haemoptysis. For the whole series of cases the average duration was 10·9 months, a figure which may be compared with the average duration of 13·2 months quoted by Kidd (9) in 1883. Although we are beginning to be able to treat these cases with some prospect of success, the present average duration of life appears actually to be less than it was nearly half a century ago. We also

compared the average duration in the four main types and found that it was exactly the same, i. e. about 11 months in each. It would seem, therefore, that the direction and extent of infiltration have no influence upon the prognosis as far as length of life is concerned.

Symptomatology. The *onset* was sudden in no less than twenty-five of the cases and insidious in the remaining seventy-five; in the majority of the cases the initial symptom implicated the chest, but on some occasions the local condition remained quiescent, and attention was only drawn to its presence by the occurrence of symptoms as a result of metastasis.

The mode of onset can be best appreciated when reviewed in tabular form.

I. *Acute Onset of Symptoms.*

(a) *Thoracic*		(b) *Extrathoracic*	
'Influenza'	in 9	Hemiplegia	in 1
Pleurisy	„ 5	Diplopia	„ 1
Cough	„ 5	Perforation of ileum	„ 1
Pneumonia	„ 2		
Haemoptysis	„ 1		

II. *Gradual Onset of Symptoms.*

(a) *Thoracic*		(b) *Extrathoracic*	
Cough	in 37	Paraplegia	in 2
Pain	„ 15	Oedema of face	„ 2
Dyspnoea	„ 9	Oedema of arm	„ 1
Dysphagia	„ 1	Pain in lumbar region	„ 1
Aphonia	„ 1	„ „ hip	„ 1
		„ „ neck	„ 1

In addition there were four cases in which the first symptom was lassitude and general malaise, the result of the presence of a malignant growth, without localizing symptoms.

Analysis of main symptoms. As would be expected, *cough* was by far the commonest symptom, being noted in ninety-one of the cases at some stage or other of the disease, and being the initial symptom in forty-two of the cases. In two cases in which a small mass of growth was present in a main bronchus, with little change in the lungs, cough was a negligible symptom, whereas cough was a prominent feature of those cases in which superadded infection or bronchiectasis was present; and it would appear that, in the early stages at least, cough results not so much from the presence of the carcinoma as from the secondary changes which it induces. With larger tumours and extensive bronchial invasion, particularly in cases where the growth was beginning to invade the lower end of the trachea, severe paroxysms of very distressing cough were frequently noted; occasionally this type of cough was associated with pressure on the trachea from the outside, either as a result of metastases in the lymphatic glands or, more frequently, in the Type III and Type IV tumours, where a large mass of growth directly infiltrated the mediastinum.

The most typical variety of cough is that described in the text-books as 'brassy', and twelve examples of this were discovered. In each case there was a large mass of growth present in the mediastinum, and the pressure of such a tumour upon the lower end of the trachea, without necessarily any direct

invasion of its wall, would appear to be the cause of this type of cough. In ten of the cases the cough became husky and ineffective in the later stages of the disease, and this change was invariably associated with laryngeal paralysis. This change in the character of the cough is therefore an indication of advancing mediastinal infiltration.

The severe paroxysms of coughing were frequently associated with acute pains in the chest, headaches, insomnia, and vomiting; transitory oedema of the face and upper limbs were also occasionally present. It is surprising to note that in no less than nine of the cases there was no mention of cough as a symptom throughout the whole course of the disease.

Sputum. It is highly probable that there was sputum present at some stage of the disease in all of the cases in which cough was a symptom. The sputum was, however, sufficient to cause comment in seventy-three of the cases, in some of which it varied according to the stage of the disease. According to the type of sputum produced, four main groups could be separated:

Sputum.	Cases.
Clear Mucoid . . .	6
Mucopurulent . . .	12
Blood streaked . . .	37
Frank blood . . .	18

It is a striking feature that blood was present in the sputum in no less than fifty-five of the cases, and this is a point on which considerable diagnostic significance can be placed. The amount of blood coughed up varied from a few streaks on one or two occasions to a very large haemoptysis which proved rapidly fatal.

In none of our cases was there any mention of the presence of the typical 'red-currant jelly' sputum, emphasized in the text-books.

Pain is commonly present at some stage of the disease, and was noted in fifty-nine cases. It was the very first symptom in fifteen of the cases which commenced insidiously, and was also prominent in a large proportion of the sixteen cases which began with acute symptoms in the chest. Although often a prominent symptom, it may be entirely absent throughout the course of the disease. The pain is usually situated in the chest, although it may be present in other regions of the body as a result of metastasis.

The commonest cause of the less severe and more chronic forms of chest pain appears to be the strain of coughing, and is presumably the result of muscle spasm; involvement of the pleura by the main growth or by secondary deposits and coincident chronic pleurisy are also frequently met with as causes of this type of pain. The more severe varieties are usually to be explained by the occurrence of acute pleurisy overlying the growth or by infarction of the lung.

It must, however, be remembered that localized pain may result from erosion of the bony chest wall, as occurred in five of our cases, with invasion of the intercostal nerves, or from the presence of secondary deposits within the spinal canal pressing upon the posterior nerve roots or even upon the cord itself.

The pain in these latter cases is exceedingly severe and of a girdle distribution, being exactly similar to that of a primary tumour arising in connexion with the spinal cord. Root pains of this type were a feature of five cases, and in this connexion it may be noted that herpes zoster was present on two occasions. Pain may also occur in other parts of the body as a result of secondary deposits interfering with nerve plexus or peripheral nerves. This was not, however, a very common occurrence, the regions affected being the brachial plexus in three cases, the cervical and lumbar plexus in two cases, and the lumbar muscles and hip joint in one case each.

Night sweats were present in fifteen cases, and there was no special feature of this symptom which calls for comment.

Dyspnoea. The term is used here in its literal significance of difficulty in breathing, and is consequently confined to those cases in which this was actually the complaint of the patient; there is no connexion between the degree of dyspnoea present and the actual respiration rate as recorded on the charts, and the latter will be considered separately in its proper place. Dyspnoea was present in seventy-three cases, but in only nine of these was it the initial symptom, and in the majority of the cases it was almost terminal. In some cases it was clearly the result of a rapid accumulation of fluid within the pleural cavity, and on one occasion accompanied the onset of a spontaneous pneumothorax; in several cases it was associated with a severe degree of pressure on the trachea from a mediastinal mass.

We are not convinced that dyspnoea was ever, in this series of cases, the direct result of extensive lung destruction, or even of occlusion of one main bronchus. It appeared from a comparison of the clinical and post-mortem notes that there was no relation between the degree of dyspnoea and the amount of involvement of lung tissue, and we have reached the conclusion that dyspnoea depends upon the rate of development of the interference with the respiratory functions rather than upon the actual extent of the lung involvement. In other words, the more rapidly the tumour is progressing the more probable is it that dyspnoea will be present. As would be expected, dyspnoea was also a marked feature of the acute inflammatory complications of the condition, as well as of the terminal pulmonary oedema which is so common in this condition. Inspiratory stridor was found to occur in four cases, in all of which the trachea was markedly compressed by surrounding growth.

Other symptoms of intrathoracic pressure. Dysphagia was present in eleven cases, and was nearly always a late manifestation of the disease, although in one case it was the earliest symptom of which the patient complained. Voice changes, varying from slight huskiness to complete aphonia, were present in twenty-one cases, in one of which loss of voice was the earliest symptom. In each of these cases in which the larynx was examined there was paresis or paralysis of one of the recurrent laryngeal nerves, the left being affected more commonly than the right in the proportion of eleven cases to five. The occurrence of oedema, as a result of obstruction to the great veins in the thorax, was

not uncommon, and was the earliest evidence of disease in three cases. This question of oedema will, however, be considered later in the section which deals with physical signs.

Symptoms of metastasis. A common symptom of this type is pain, the incidence of which has already been considered. Vomiting was a marked feature in seven cases, in some of which there was considerable abdominal metastasis, and in one of which a large haematemesis occurred as a result of erosion of the stomach by a deposit of growth. Vomiting occasionally appeared to result from the strain of severe paroxysms of coughing, and was associated with cerebral deposits in two cases.

The most interesting and perhaps the most important group of cases in which extrathoracic secondary deposits gave rise to prominent symptoms were those in which the central nervous system was involved. This occurred in fifteen cases altogether, the brain being affected in eleven, the spinal cord in four. In the latter group paraplegia was present in three of the cases, in two of which it brought about symptoms before the intrathoracic neoplasm had been discovered; in the fourth case severe root pains were complained of, but paralysis did not supervene.

The general symptoms of intracranial pressure, headache, and vomiting occurred in two cases, and severe headache alone was present on one occasion. Epileptiform convulsions were noted in five, mental changes in three cases, and diplopia twice. The mental changes consisted in increasing slowness of cerebration, associated with torpor and a dreamy state, progressing slowly to a coma, in which condition the patients died. Hemiplegia was present in three cases; and it may be mentioned that in one other case, in which several small deposits were found in the brain *post mortem*, there had been no clinical evidence of cerebral involvement during the patient's life.

In addition to these symptoms indicative of local organic disease, the common cachectic manifestations of malignant disease were present, and some degree of loss of weight occurred in sixty-two of the cases; this point will be dealt with in the section on physical signs.

The physical signs. The physical signs of the disease in the chest were naturally found to vary enormously, and it is therefore impossible to describe more than the general types of change which were found to occur.

Distribution. It is generally agreed that both sides of the bronchial tree are equally liable to be affected, and in this series the primary growth took its origin in the right bronchus in fifty-two of the cases and in the left bronchus in the remaining forty-eight. The growth arose in a main bronchus in sixty, in an upper division in nineteen, and in a lower division in seventeen; in addition, the bronchus supplying the right middle lobe was affected twice, and on two other occasions the growth appeared histologically to spring from a bronchiole and could not be definitely shown to be in connexion with any of the larger bronchi.

Wasting was not quite so marked, on the whole, as would have been

expected. Thirty-eight of the patients showed no loss of weight at all, thirty-two had lost a certain amount of weight, and in thirty only was the wasting at all severe.

Clubbing of the fingers was noted in eighteen of the cases, and in one case there was an extreme degree of hypertrophic pulmonary osteo-arthropathy. There was no definite association in these cases with bronchiectasis nor with chronic suppuration of any sort, and it appears that clubbing can occur as the result of bronchial carcinoma alone. It is probable that minor degrees of clubbing escaped record in some cases, so that these figures represent a minimum estimate of the incidence of this condition.

Temperature. It is difficult to convey any exact impression of the temperature in these cases as so many factors may influence the form of the charts from stage to stage of the disease. In fifty-seven of the cases there was no rise of temperature throughout the course of the illness, and in the remaining forty-three there was pyrexia of varying degree at some period.

The fever varied in a completely irregular manner, being on the whole less than 100° in thirty-one of these cases and of greater degree in the remaining twelve. Yet the temperature chart did not appear to bear any strict relationship to the degree of acute inflammatory change which had occurred as a complication, and we have accordingly considered the matter more fully, comparing the clinical notes with the actual condition found *post mortem*. The results of this survey are as follows:

	Febrile.	Afebrile.
Pneumonia	11	13
Lung abscess	6	6
Gangrene	5	1
Empyema	6	4
Active phthisis	5	7
Other inflammatory complications	4	3

It can be seen that, even with pus formation in the chest, there need be no rise of temperature at all, and we may also mention that, conversely, fever may occur in cases of bronchial carcinoma in the absence of any inflammatory focus. The additional inflammatory complications to which reference is made above include cases of pericarditis, peritonitis, and cystitis. The temperature is therefore of little diagnostic or prognostic significance when considered alone, and little weight can be safely placed upon it when considering any individual case.

Pulse. Many factors influence the pulse frequency, and consequently no diagnostic significance can be attached to this, although naturally information of prognostic value may be obtained by examination of the character of the pulse. We found that the pulse frequency varied as capriciously as did the temperature in relation to the physical conditions present, but that with fever there was invariably a raised pulse-rate. In seventy-three of the cases the frequency was greater than 90 per minute at rest, and in the remaining twenty-seven it was below this rate. We found also that a normal pulse-rate could be associated with the more chronic forms of lung abscess, whereas a raised pulse-

rate occurred in seventeen cases in which the carcinoma was not complicated by any infection.

There was no evidence in these cases to suggest that the tachycardia was the result of infiltration of the vagus, and although this possibility could not be excluded it seems more probable that the increased pulse frequency is the result of toxaemia occurring in connexion with the growth. A mild degree of bradycardia was present in the later stages of two of the cases in which cerebral deposits were present.

Respiration rate. It has already been pointed out that the actual frequency of respiration has no connexion with dyspnoea, and the respiration-rate was found to be raised above 25 per minute in fifty-eight of the cases, whereas it was below this figure in the remaining forty-two. In nearly every case, however, there was considerable increase in the respiration-rate within the last two or three days of life, the result of terminal bronchitis, pulmonary congestion, or hypostatic pneumonia. In many instances the respiration-rate was found to be constantly increased quite apart from the presence of any inflammatory complication, and this occurred no matter whether the main mass of growth was confined to the lung or to the mediastinum. At the same time it must be pointed out that an increased respiration-rate was not usually associated with chronic respiratory obstruction, in which type of case dyspnoea was frequently a prominent symptom ; it was indeed a striking feature of such cases that the respiration-rate was normal in spite of marked difficulty in inspiration. It would seem probable that tachypnoea at rest, which was of fairly frequent occurrence, is partly the result of some interference with the nervous control of respiration, perhaps acting through the Hering-Brauer reflex, and its presence is, therefore, a point of some diagnostic significance.

Cyanosis. Cyanosis was not so commonly present as might have been expected. It was an early sign in sixteen cases, and was in most of these the result of obstruction to the trachea combined usually with some degree of obstruction to the great veins. Simpson (17) regards cyanosis in these cases as primarily the result of venous obstruction, but we found that oedema, which was invariably associated with venous obstruction, was much commoner than cyanosis, and quite frequently occurred apart from the latter, whereas the cases in which cyanosis was a marked feature usually showed marked obstruction of the trachea *post mortem.*

In the later stages cyanosis occurred more commonly, being then usually the result of one of the terminal complications of the disease.

Oedema. Oedema may occur locally in the chest wall, in the face, neck, and arms, or it may affect the abdomen and legs, according to the situation of the obstructing mass of growth. Occasionally *post mortem* the growth was found actually to have infiltrated the great veins, at other times the oedema appeared to be due to pressure on the veins with or without thrombosis. It occurred altogether in thirty of the cases, in three of which it was the initial manifestation of the disease. The distribution was naturally very varied,

affecting either side or both sides according to the situation of the obstruction. Oedema of the face, neck, and both arms, as a result of obstruction of the superior vena cava, occurred on four occasions: oedema of the right arm with some involvement of the face occurred four times, while oedema of the left arm and face were noted twice only.

The face and neck were, however, involved without the arms in fourteen other cases, and it appeared that the looser subcutaneous tissues of these regions tended to the development of oedema as a result of slighter degrees of venous obstruction than did the firmer tissues of the arms.

Local oedema of the chest wall overlying the growth usually occurred as a result of direct infiltration of the parietal pleura and was present in four cases; the abdominal wall and legs were found to be oedematous in a further two cases, apparently as a result of pericardial involvement with obstruction of the inferior vena cava; in both of these cases ascites was also present. In a further case oedema of the legs was present as the result of heart failure, but this is not included in the list of cases in which oedema was present as a sign of intrathoracic malignant disease.

Dilated veins. Dilated veins were present in the majority of the cases in which there was marked oedema, and the two groups of cases show a close correspondence. Altogether they were noted on twenty-seven occasions, the veins of the thoracic wall being involved in twenty-one cases, most commonly only on the affected side, the cervical veins in five, and the abdominal veins in one case only.

The significance of these two latter signs is essentially similar, although venous dilatation frequently preceded oedema. In each case they indicate definite obstruction to the return of blood through the great veins in the mediastinum, and malignant growth is by far the commonest cause of this condition.

Laryngeal paralysis. The effects of interference with the recurrent laryngeal nerve upon the voice and upon the type of cough have already been discussed.

The larynx was known to be affected in sixteen of the cases, the left side being paralysed in eleven and the right side in five cases.

Sympathetic paralysis. Inequality of the pupils ascribed to this cause was observed in four cases. The complete syndrome, including ptosis and exophthalmos, was not, however, present; the majority of authors have found that sympathetic involvement is rare in this condition.

Diaphragmatic paralysis. There was not sufficient clinical or post-mortem evidence to deduce the frequency of involvement of the phrenic nerve, and we have consequently been compelled to rely upon the reports of the movement of the diaphragm when viewed upon the X-ray screen.

In many cases, not even this evidence was available, either because the patients had been too ill to be screened or owing to the loss of the X-ray reports.

In twelve cases the diaphragm was seen to move normally, in sixteen it was seen to be immobile, presumably as a result of phrenic nerve paralysis, and in twenty cases its state of activity could not be observed owing to the presence of dense shadows in the lower part of the chest. In a further fifteen cases the report made no reference to the activity of the diaphragm, and it is unlikely that in these cases the presence of paralysis would have escaped comment.

Other pressure phenomena. Pressure on the vagus nerve is held by some to account for paroxysmal dyspnoea, cough, vomiting, and tachycardia. It is difficult to obtain proof of this, yet as an explanation of some of these phenomena the theory appears to be satisfactory, and, in so far as the respiration-rate is concerned, we believe this explanation to be probably correct. Unfortunately there was not sufficient evidence in the post-mortem notes for us to be sure of the condition of the vagus nerves in the majority of cases, so that we must leave this explanation open to further discussion. There was no note in any of the cases in this series of inequality of the pulses as a result of compression of the aortic arch, although in some cases the distortion of the vessel was severe. It must be remembered, however, that pressure upon the vessel is very different from the condition which occurs with aneurysm, in which there is likely to be a loss of pressure owing to the sudden increase in the width of the lumen of the vessel, and we regard this sign in malignant disease as being of theoretical rather than of practical importance.

Physical signs in the chest. The physical signs varied very much in the different cases, according to the situation and mode of spread of the primary growth, and according to the stages of the disease. We propose to consider first the physical signs which were present on the earliest date of examination. In brief they may be classified as follows :

of pulmonary consolidation	45
of mediastinal tumour with pulmonary collapse	22
of pleural effusion	16
of pulmonary collapse	8
of cavity	2
of bronchiectasis	2
of bronchitis	2
of pneumothorax	1
physical signs indefinite	2

It is clear from this table that the majority of cases were far advanced before they first came under observation, so that these by no means represent the early signs of the disease, although they afford some clue to the type of physical signs which may be met with in early cases. The signs of consolidation are very commonly present at the time of the first examination, although this does not necessarily imply that there is extensive infiltration of the lung, for much of the consolidation may be inflammatory, and these physical signs may be actually found to decrease for a time at least. This particularly applies to those cases in which there has been some recent inflammation in the lung tissue distal to the growth diagnosed variously as pneumonia, broncho-pneumonia, or influenza. As would be expected, the signs of collapse, as a result of

bronchial obstruction, were also commonly found in the early stages. In many of these, however, there were already the signs of mediastinal involvement, impairment of percussion note behind the sternum or in the interscapular space with bronchial breathing, bronchophony, and the extrinsic signs of mediastinal pressure. The other common early signs were those of liquid effusion into the pleura, which appears to be quite an early complication of this type of growth.

As the disease progressed, so also did the physical signs increase, although on the same lines as those already mentioned, and terminally those of pneumonia, broncho-pneumonia, or bronchitis were frequently superadded. It is not proposed to trace the progress of these cases in detail, as the importance of physical examination concerns early diagnosis, on which chief emphasis must therefore be laid.

Accordingly, we propose rather to review the early signs in the order in which physical examination of the chest is usually made. As the cases came under observation at widely different stages of the disease, it is necessary to discuss them in general terms in order to avoid possible misconception.

Inspection. As a rule there was little abnormality in the shape of the chest in the early stages of the disease. Local wasting was noted in one-fifth of the cases, in only two of which was it a prominent feature. On the other hand fullness on one side was noted in four cases as a result of the presence of a massive tumour, and was present to a lesser extent in several of the cases in which there was considerable pleural effusion. In one case there was a local swelling of the chest wall due to actual infiltration of the intercostal spaces and subcutaneous tissues by the underlying tumour.

On the other hand diminished movement was one of the earliest physical signs in nearly one-half of the cases. Dilated veins were not a common early sign, and usually began to appear at a later stage of the disease.

Palpation. Local tenderness was not present in any of the cases. The vocal vibrations were not sufficiently constantly altered to yield any evidence of diagnostic value. Expansile pulsation was noticed on one occasion, and a diagnosis of aneurysm was made, to be disproved *post mortem.*

The chief value of palpation, associated with percussion, was the determination of the position of the heart. It was found that the heart was in its normal position throughout the course of the disease in sixty-six of the cases. In the remainder it was but little altered in the earlier stages, so that as an early diagnostic sign cardiac displacement does not appear to be of much value. Displacement of the heart towards the affected side occurred in only thirteen of the cases, in the majority of which it was the result of pulmonary collapse, and not of any chronic process of fibrosis. Displacement towards the sound side occurred in the remaining twenty-one cases, being the result of liquid pleural effusion in eighteen, and of massive growth in three; there was no displacement in the case associated with pneumothorax.

Percussion. The percussion note varied according to the site of the

primary tumour and its mode of spread. In the root tumours there was frequently no impairment of percussion note although the air entry into the affected part of the lung was considerably diminished. With more superficial growths, however, some degree of impairment was nearly always present, and with liquid effusion there was the customary dullness. Retrosternal dullness was fairly commonly noted in cases with marked mediastinal involvement. The usual percussion changes of liquid effusion were present in twenty-four cases, in sixteen of which the signs were present on the first occasion on which the patient was examined.

Auscultation. It is really on auscultation that the early diagnosis of bronchial cancer depends. With even an early lesion of the bronchus there is frequently some degree of spasm of the bronchial muscle fibres with consequent constriction of the tube in excess of the obstruction produced by the growth; this point will be further discussed when the X-ray appearances following lipiodol injection are considered. In consequence of the obstruction the air entry is diminished on the affected side, and in our series this sign appeared to be present even in the cases which were in an early stage of development. Pleural friction was an early sign in no less than seven of the cases. Added sounds produced in the lung itself were not usually present, unless there was some superadded acute or chronic inflammatory condition.

From this summary of the early physical signs it can be seen that there are no physical signs which are pathognomonic of bronchial carcinoma, and it would seem that in the early stages the diagnosis must for the present depend upon the careful application of accessory methods of investigation in all cases in which there is any possibility of carcinoma.

A definitely diminished air entry in any localized area of the chest in an adult, in whom its presence cannot be easily accounted for, should always be regarded as suspicious of malignant disease, and all possible steps should be taken to exclude its presence.

There is, however, one point of importance which emerges from a consideration of the physical signs of these cases. In the majority of cases the physical signs of bronchial carcinoma are confined strictly to the affected side, and this occurred in ninety-two of our cases. Bilateral physical signs are much more suggestive of a chronic inflammation than of a growth.

In twelve cases post-mortem examination revealed the presence of active tuberculous lesions in addition to the growth. In these cases the physical signs were frequently bilateral and râles and crepitations were usually present. The presence of these tuberculous lesions, if fully confirmed, is apt to cause the more serious condition to pass unrecognized, in the early stages at least, and only careful consideration of the history, symptoms, and clinical findings can give a clue to the real state of affairs. At the same time the fact that active tuberculosis was found in only twelve cases out of 100 lends no support to the theory that bronchial cancer is connected aetiologically with pulmonary tuberculosis.

Clinical metastases. Although post-mortem examination revealed their presence in ninety cases, secondary deposits were only detected during life in fifty of these. It is obvious that many deep-seated sites of deposit must be overlooked by the clinician, and this is a point of difficulty in assessing the variety of treatment to be adopted in any given case.

A comparison of the clinical and post-mortem findings is given in the form of a table which deals only with the commoner sites of deposit.

Site of Secondary Deposits.

		Found *Post mortem.*	Detected Clinically.
1.	Mediastinal glands	82	uncertain
2.	Cervical glands	28	20
3.	Axillary glands	14	12
4.	Abdominal glands	41	3
5.	Liver	33	9
6.	Suprarenals	20	0
7.	Pancreas	13	3
8.	Peritoneum	5	2
9.	Small intestine	4	1
10.	Stomach	2	1
11.	Brain	11	10
12.	Spinal cord	4	4
13.	Cutaneous	8	8

The secondary deposits which occur commonly may be classed in three main groups—the glandular, the visceral, and the cerebral. The lymphatic glands usually affected were the regional nodes of the tracheobronchial group, although the cervical nodes were affected in twenty-eight, and the axillary in fourteen cases. The upper abdominal glands were also quite commonly involved, most probably by a direct lymphatic spread, and it is noteworthy that, in almost all cases in which there were deposits in the larger abdominal viscera, the regional abdominal nodes were also found to be involved, the inference being that the majority of abdominal metastases occur as a result of lymphatic rather than of blood-stream dissemination.

It is not generally realized that abdominal metastases are common in bronchial carcinoma, and yet they were present in sixty-one of the cases.

The liver, suprarenals, and pancreas were the organs most commonly involved, although the kidneys, ureters, peritoneum, and mesentery were also occasionally the site of deposit. The alimentary tract was rarely involved; on two occasions there were nodules of growth in the stomach, and in four cases there were nodules in the ileum, near the ileo-caecal valve. In one of these latter cases perforation of the bowel occurred and death resulted from acute peritonitis; in the remainder the presence of the metastases was not recognized during life. On no occasion were any symptoms of intestinal obstruction present.[2]

In three of the cases in which the liver was found to be involved the deposits were massive and the organ weighed between 100 and 250 ounces. In

[2] W. G. Barnard and T. R. Elliott have recently described in this Journal (1930, xxiii, p. 407) two cases of primary bronchial carcinoma in which acute obstruction occurred as a result of intestinal metastasis.

the remainder the liver was comparatively little enlarged and contained varying numbers of small rounded deposits. It is curious to note that jaundice, which occurred as a terminal event in five cases, was never the result of direct involvement of the liver, no matter how massive the deposits and how little functional liver tissue remained undamaged. In every case in which jaundice occurred there was found to be organic obstruction of the common bile duct, either by a deposit in the head of the pancreas, or by enlarged glands in the hilum of the liver.

It must be noted, however, that not all of the cases in which secondary deposits were detected clinically were correctly diagnosed. In several a deposit was considered to be of primary growth, and the pulmonary involvement was erroneously presumed to be secondary.

With respect to the involvement of the central nervous system, it frequently happened that this was not examined *post mortem* when there had been no obvious cause during life for this to be done, so that the post-mortem figures in this case cannot be regarded as absolute.

Cutaneous metastases were not uncommon, being found on eight occasions. The main importance of this fact is that a bronchus should always be considered as a possible primary source in cases in which metastases are detected in or under the skin. In all of these cases the nodules were small and shotty, the largest of all being less than 2 cm. in diameter and the average very much less. The usual distribution was the front and back of the chest and shoulders, and the anterior abdominal wall surrounding the umbilicus. Although it is possible that these were the result of lymphatic rather than blood-stream spread, yet in one case the main incidence of the nodules was in the scalp, which would favour the latter method of dissemination. In no case did these cutaneous metastases break down or ulcerate.

Additional Methods of Investigation.

Sputum. The frequent occurrence of blood in the sputum has already been the subject of comment, along with the other naked-eye appearances.

The results of routine bacteriological examination yielded no significant results. Examination for tubercle bacilli, however, was performed in the great majority of the cases, and the organisms were discovered on six occasions. This fact must be borne in mind, for it is easy to assume, on the discovery of tubercle bacilli in the sputum, that the condition is one of pulmonary tuberculosis, and so to adopt unnecessary, although perhaps innocuous, lines of treatment.

The discovery of malignant cells in stained films of the sputum is proof positive of the presence of a malignant growth. Unfortunately, owing to the difficulty of recognition, their presence is rarely reported, and they were found in one case only in this series.

Pleural effusion. Fluid was withdrawn from the chest for examination in twenty-four cases during life, and in twenty-two additional cases collections

which had either not been detected or in which paracentesis was not indicated were disclosed *post mortem*.

The general nature of these effusions was as follows:

	Found during Life.	Found *Post mortem*.	Total.
Clear fluid . . .	11	10	21
Blood-stained fluid .	8	7	15
Empyema . . .	5	5	10

The post-mortem effusions were nearly all less than ten ounces in quantity, and the empyemata in particular were small encysted collections of pus towards the base of the lung or in an interlobar fissure, which would not have been likely to cause definite physical signs. Their bacteriology was not noted in most of the cases.

The cytological changes in the fluid are of more importance, although in many cases they do not afford information of diagnostic import. It was noted that red blood cells were usually present in the specimens of clear fluid on microscopical examination, although not sufficiently constantly to prove of value in diagnosis.

The cell content of the fluid was only included in the notes of those cases in which paracentesis had been performed—a total of fifteen cases, excluding those in which frank pus was found. In four of the cases no note on the cytology was available. Polymorphonuclears were predominant in four, lymphocytes in nine, and endothelial cells in the remaining two.

Typical Foulis cells were stated to have been present in six of the cases, in two of which endothelial cells predominated, and in the remainder lymphocytes.

These cells are large multi-nucleated and vacuolated cells which are probably formed as a result of irritation of the pleura and are not themselves derived from the growth. At the same time the presence of Foulis cells, if beyond doubt, appears to be good evidence of a malignant growth involving the pleura. Otherwise, examination of the pleural fluid does not yield any evidence which will distinguish the effusion of malignant disease from that of tubercle or of lymphadenoma.

Blood count. Anaemia was not a prominent feature of the disease. Accepting a definition of figures below four million red cells per cubic mm. and 80 per cent. of haemoglobin as our criterion, anaemia was only present in eighteen of the sixty-three cases in which the blood count was recorded, and was never very severe.

The white blood count showed more constant changes, although fluctuations occurred from stage to stage of the disease, and we have therefore been compelled to adopt an average figure in some instances. The following table summarizes the findings:

W. B. C.	
Below 5,000 per cu. mm.	1
From 5,000 to 10,000 per cu. mm. . . .	13
From 10,000 to 20,000 per cu. mm. . . .	39
Over 20,000	10

Thus it is seen that leucocytosis occurred in the majority of cases; the polymorphs were the cells which were increased. On further analysis it did not appear that the leucocytosis was merely the result of an infective complication, for it was present in twenty cases in which no marked infection was present, and on the other hand the white cells were below 10,000 per cubic mm. in six cases in which there was actual pus formation within the chest. This is a point which must be borne in mind in making the difficult differentiation between chronic lung abscess and carcinoma, for leucocytosis does not necessarily indicate pus formation, nor does its absence exclude it.

The Wassermann reaction. Just as the sputum may contain tubercle bacilli in bronchial carcinoma, so may the Wassermann reaction indicate the presence of syphilis. The reaction was positive in fifteen out of sixty-two cases, in only one of which was there gumma formation in the lung. The reaction is therefore apt to mislead, and should be entirely discounted if the other evidence points in even the least degree to the presence of carcinoma.

X-ray examination. The X-ray appearances of bronchial carcinoma may be extremely diverse, and we do not feel that it is within our province to discuss the question in detail.

It is only quite recently that it has been realized that in lipiodol we have a valuable diagnostic aid in cases of suspected bronchial disease, and consequently the number of cases in which this investigation was attempted is small. In the very early cases it is probable that the X-ray film taken after the insertion of lipiodol might show a slight irregularity only of the bronchial contour. Only one of these cases, however, was investigated sufficiently early to obtain this result. In later cases the common finding is complete blockage of the affected bronchus, and this was found on five occasions.

In three of these, seen personally by one of the writers, there was not complete obstruction of the affected bronchus when the local condition was investigated *post mortem* some weeks later, although the obstruction on the X-ray film was absolute. The only feasible explanation of this finding is that there is a protective spasm of the sound bronchial muscle on the proximal side of the lesion which reflexly protects the injured area from exposure to foreign material.

Furthermore, we have no evidence, from the notes of these cases nor from our own experience, of a normal lipiodol filling occurring in a case which proved to be one of bronchial carcinoma, and we consider that this investigation is of the utmost diagnostic value in the investigation of suspicious cases of this nature.

Bronchoscopy. In none of our cases was any assistance obtained from bronchoscopy, for a negative result was obtained in each of the five cases in which it was attempted. Theoretically at least, direct inspection should be of great value in diagnosis, and this operation should be undertaken more frequently in order to ensure a diagnosis being made at the earliest possible moment.

Histological appearances. The diagnosis of carcinoma was made in eight cases on the microscopical appearances of material removed for section during life, cervical and axillary glands and skin nodules being the tissues most com-

monly selected for removal. In two cases the diagnosis was made by direct exploration of the lung, although at operation on three others the diagnosis was overlooked owing to the finding of pus in the lung or pleura with the consequent assumption of the presence of a lung abscess or empyema. In two further cases material removed at operation showed inflammatory changes only, although a carcinoma was subsequently proved to be present.

Results of Treatment.

As we have already pointed out, the majority of these cases first present themselves for diagnosis at a comparatively late stage of the disease, and consequently palliative measures only can be adopted.

Treatment directed to the growth itself may be by means of X-rays, radium, or surgical operation, and the first method only was employed in this series. None of these methods is ideal in dealing with intrathoracic tumours, for it is not possible to gauge the presence or extent of early secondary deposits in the chest or abdomen and therefore to eradicate the disease with that certainty which is possible in the earlier stages of malignant disease in many other parts of the body.

Sixteen cases were treated by means of X-rays, each receiving more than ten applications. Several other cases received fewer applications than this and are not considered further. The average duration of the cases so treated was fourteen months as compared with an average of 10·9 months for the whole series. In four of these the treatment may have prolonged life, in the remainder it was impossible to conclude that much benefit had been conferred. Furthermore, in three cases there was little doubt that the application of X-rays had caused a rapid dissemination of the growth with a fatal termination much sooner than would have otherwise been expected. On the whole, therefore, the results of X-ray treatment are not encouraging, and our results are in agreement with the view of Edwards (6), who states that he has not seen definite improvement, much less cure, in any case of bronchial carcinoma treated by X-rays. With regard to the histological type, nine of the sixteen cases were basal-celled tumours and seven were ordinary carcinomata. Although the total number of each was small it could not be found that either type reacted better to X-ray treatment than the other; this point might be used as an additional piece of evidence in favour of the view that the 'oat-celled' tumour is a basal-celled carcinoma and not a sarcoma, for sarcomata, as a whole, react distinctly better to X-rays than do carcinomata.

X-ray treatment may also be of use in differentiating certain kinds of growths. Failure to react to heavy doses of X-rays by shrinking in size is strong evidence that the growth is a carcinoma. Sometimes a carcinoma reacts quite well, for a time, but even then it does not do so until a considerable dose has been given.

No other methods of treatment were employed, and therefore we express no opinion as to their value.

We have already indicated that these tumours can be separated into four groups by study of their morbid anatomy. From the clinical point of view it seems possible that such a classification might be helpful in deciding the line of treatment to be adopted in any given case, for it is clear that surgical measures are impracticable when the mediastinum is involved to any extent, and it is important to know how far we may rely upon our interpretation of the clinical picture and radiographical appearances in gauging the extent of the disease within the chest. We have accordingly correlated the pathological type with the clinical picture in each case in an effort to determine the reliability of the clinical evidence as a guide to the anatomical state of the tumour.

Type I. *The hilum tumour.* This variety of tumour was present in eight cases, in three of which the growth projected mainly into the lumen and in the remaining five surrounded the bronchus as a spherical mass; infiltration of the surrounding tissues was minimal.

The symptoms were not characteristic although dyspnoea was a prominent feature even with quite small growths. The usual physical signs were those of collapsed lung; the air entry was diminished early although no change in the percussion note could be detected until a later stage. In two cases the signs of bronchiectasis were present and effusion developed in two others. Metastases in the mediastinal glands were present in six of the cases, although the deposits were never so large as to be detected on clinical examination.

The diagnosis of a tumour of this type depends upon the clinical evidence of a collapsed lobe associated with the appearance of a localized mass in the skiagram and the demonstration of bronchial obstruction after the injection of lipiodol. Bronchoscopy should always be performed, for the growth nearly always arises in the main bronchus and well within the limits of visibility.

It is in the early cases of this group that surgical removal is most likely to meet with success. In the more advanced cases radium, in the form of needles or of radon seeds, may be inserted into the growth, through the chest wall, or radon seeds may be introduced into the lumen of the bronchus by means of a bronchoscope.

Type II. *The lung tumour.* Infiltration of the lung alone was present in twenty-nine cases, the commonest symptoms being cough, haemoptysis, and pain. It must be noted, however, that voice changes and dysphagia were occasionally present as a result of direct pressure of a large tumour upon the mediastinal structures without actual infiltration, so that these symptoms do not necessarily indicate mediastinal infiltration. The physical signs were those of consolidation in most of the cases, and impairment of percussion note was associated with diminution of the air entry at an early stage. Pleural effusion was not uncommon, but evidence of involvement of the chest wall, as indicated by oedema or actual infiltration of the extrathoracic tissues, was rare.

With localized tumours of this type lobectomy would appear to be indicated, and failing this radium.

Type III. *The mediastinal tumour.* In twenty-five cases the growth spread directly from the bronchus into the mediastinum. The usual symptoms were those of mediastinal pressure, harsh cough, dyspnoea, and oedema. Haemoptysis occurred in nearly half of the cases but pain was rare. The physical signs were those of a mass in the mediastinum, usually in the upper part, associated with dilated veins and obstructive oedema. The lung signs varied considerably, those of collapse being the commonest. In this type of tumour surgical treatment is out of the question on account of the early involvement of vital structures, the pericardium and great vessels being usually infiltrated from an early stage. A similar objection applies to radium, so that the only form of treatment which can be attempted is radiotherapy. The outlook for improvement in treatment in this type of tumour, even with early diagnosis, is, therefore, not so hopeful as it is in the preceding two varieties.

Type IV. *The combined tumour.* From the ordinary tendency of a malignant growth to infiltrate, it would be expected that, *post mortem* especially, combined infiltration of the lung and mediastinum would be the common finding, and this was found to be true, the combined tumour being present in thirty-eight cases. The symptoms and physical signs presented on the whole a combination of the characters of Types II and III. The lung signs were usually those of consolidation, although pleural effusion was commoner in this than in the other groups.

From the extensive nature of the infiltration it follows that radiotherapy is the only means of attack, and necessarily the prognosis is worse in this than in the other three types.

As a result of this study we have come to the conclusion that from a combined consideration of the physical signs and the radiographical appearances, it is possible to form a reasonably accurate opinion of the condition present in the chest, and consequently to decide upon the appropriate line of treatment to be adopted. As a rule it would appear that the signs of mediastinal pressure indicate definite mediastinal infiltration or else a tumour so large as to be irremovable, yet it must be realized that infiltration of vital structures may be present in an early stage without giving rise to clinical signs. On the whole, therefore, we are liable to overestimate rather than to underestimate the operability of a tumour.

Summary and Conclusions.

A series of 100 cases of proved bronchial carcinoma is recorded, and the clinical, pathological, and post-mortem findings are correlated.

The main clinical features are considered in detail, especially from the point of view of early diagnosis. It is from this standpoint alone that any

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advance in treatment can be made. The various modes of treatment which may be expected to yield results in the future are briefly considered.

The various accessory methods of investigation are considered and their diagnostic value is discussed.

Briefly stated, the steps in the investigation of a suspected case of bronchial carcinoma are as follows:

1. The history yields no sure guide; the onset of symptoms may be abrupt or gradual.

2. The symptoms are of little real diagnostic value. Cough, pain, and dyspnoea are frequent early symptoms, and haemoptysis is common.

3. The physical signs are very varied, but weak air entry over one lobe or one lung is common as an early sign. It is important, however, to note that the physical signs of bronchial carcinoma are nearly always unilateral. Metastases may be found in the cervical or axillary glands, abdomen, skin, or central nervous system. When present they confirm the diagnosis of malignant disease but also indicate that the possibility of successful treatment no longer exists.

4. The sputum seldom yields information of value. Streaks of blood are commonly present, and the presence of malignant cells confirms the diagnosis on very rare occasions. The presence of tubercle bacilli in the sputum does not negative the possibility of the co-existence of a growth.

5. Plural effusion is fairly commonly present, but is bloodstained in less than half of the cases. The general characters differ little from those of other exudates, but the occasional presence of Foulis's cells is suggestive of malignant growth, although not proof of its nature.

Empyema may occur, but it is rare.

6. The blood picture does not present any typical features. Anaemia is uncommon, but leucocytosis appears to be the rule, even in the absence of active inflammation.

7. The Wassermann reaction is misleading, and a positive result should not be allowed to influence against a diagnosis of bronchial carcinoma if there be any reasonable suspicion of its presence.

8. The X-ray appearances are usually suggestive, but only rarely can a diagnosis be made with reasonable certainty upon the appearance of the films alone.

9. Lipiodol injection into the bronchi yields information of the utmost diagnostic value. The usual finding is complete obstruction of a bronchus, although occasionally in very early cases narrowing with irregularity in the outline of the walls may be observed.

10. Bronchoscopy is an investigation which should be undertaken much more frequently. Performed by a skilled operator, and with local anaesthesia, there should be a minimum of discomfort to the patient, and by this means important information can be gained in doubtful cases concerning the actual site or origin of the growth.

11. The histological appearances of tissue removed for section are the

only certain proof of the nature of the disease. If the material be removed from the tumour by exploratory thoracotomy, the diagnosis may be confirmed in doubtful cases in time for treatment to be usefully undertaken. If a metastasis be removed a positive diagnosis is the only advantage gained.

In conclusion, we desire to express our thanks to the Medical Staffs of St. Bartholomew's Hospital and the Royal Chest Hospital for permission to make use of the clinical notes of the patients under their care, to Professor E. H. Kettle, of St. Bartholomew's Hospital, and to Dr. N. H. Schuster, of the Royal Chest Hospital, for their kindness in affording us free access to the post-mortem records and pathological material in their respective departments.

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SPONTANEOUS CARDIAC RUPTURE[1]

A REVIEW OF FORTY-SIX CASES

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With Plates 4 to 6

Spontaneous rupture of the heart, though rare, has been known to medicine for many years. The earliest extant record is a case of William Harvey's. The literature on the subject consists mainly of a large number of reports of isolated cases or very small series, published frequently by quite unskilled observers struck by the dramatic aspect of the condition. More authoritative accounts have been published by Quain (1), by Robin and Nicolle (2), and others, whilst in 1925 Krumbhaar and Crowell (3), in an admirable paper, analysed twenty-two cases of their own and reviewed the whole of the literature, a total of 654 cases. In 1928 Davenport (4) published a short addendum to Krumbhaar's work containing ninety-two further cases.

From these last two reviews the following generalizations may be made:— Spontaneous cardiac rupture is chiefly an accident of senility. It most frequently occurs in an area of recent infarction following coronary occlusion. The common post-mortem diagnosis of 'fatty degeneration' as the underlying cause is not borne out by careful histological examination.

The material here presented is a series of forty-six cases of rupture occurring at Tooting Bec Hospital since its opening in 1903. The large size of the series is due to the fact that the hospital is almost entirely devoted to senile patients, in whom cardiovascular disease is very frequent. In examining the series it has to be borne in mind that this is primarily a mental hospital, and accurate medical histories and case records are difficult to obtain from our patients. For purposes of description here the total cases have been divided into a first series of thirty-two cases occurring before accurate histological examination was possible (Series A), and a second series of fourteen recent cases which were fully examined (Series B).

Incidence. A complete survey of our death registers is unfortunately impossible, but the figures since 1920 have been analysed and are given in Table I.

[1] Received June 17, 1930.

TABLE I.

Patients Aged 60 Years or over Dying from Jan. 1, 1920—June 30, 1930.

Patients.	Deaths.	*Post mortem.*	*Post mortem* %.	Rupture.	Ruptures %.
Males	1704	971	56·98	6	0·35
Females	1904	1403	73.68	25	1·36
Totals	3608	2374	65·79	31	0·86

The figures show that, in senility, cardiac rupture, though uncommon, is by no means so rare as is usually thought. Moreover, the incidence increases with advancing years, as is shown in Table II, the highest figure being reached in the eighth decade, after which the rapid decline is probably due to the small number of patients who survive beyond that age.

TABLE II.

Age Distribution. (*Total Cases.*)

Decade.	Number.
50–60	2
60–70	3
70–80	25
80–90	13
90–100	2

Cardiac rupture is commonly stated to be much more common in men than in women. In our experience the exact opposite is the case, and even allowing for the present bed ratio in the hospital of two females to one male, which is the highest we have ever had, the figures in our series would represent a complete reversal of Krumbhaar's and of Davenport's statistics.

TABLE III.

Sex Distribution. (*Total Cases.*)

	Ours.	Per cent.	Davenport's Review.	Per cent.
Male	8	17·8	355	58·1
Female	37	82·2	257	41·9

In Table I, where the incidence of cardiac rupture during the past 10½ years is expressed as a percentage of the total deaths, the figures are far more striking, showing a proportion of almost four females to one male. A possible factor is the frequence of obesity in senile women with the accompanying likelihood of excessive cardiac fat; whilst the factor of syphilis, which has to be considered in Krumbhaar's younger patients, would tend to increase the male figures in his series.

The frequent association of insanity with cardiac rupture is remarkable. In Krumbhaar's review of the literature of 654 cases 47, or 7·2 per cent., were insane. For this he suggests the common factor of arterial disease as an explanation. A further explanation, at least in this country, is the stricter inquiry into the deaths in mental hospitals even of known cardiopaths, whereby autopsies are performed upon cases which in the outer world are certified as due to 'heart disease' and 'syncope'.

It is not impossible that there is some connexion between the excessive

mural fat which is so common in our autopsies at this hospital and such an important factor in rupture, and some obscure disturbance in metabolism, whose importance in the senile psychoses is beginning to be suspected.

Pathological Basis.

In Series B, of fourteen cases, all of which were examined histologically, every one showed recent infarction. With this essential fact in front of us we are justified in describing recent infarction as the pre-eminent cause of heart rupture, with aneurysmal dilatation a poor second. In one case 7, (AW/40), there was an aneurysm at the apex with rupture at its edge through a recently superimposed area of necrosis.

In the earlier Series A, of thirty-two cases where the heart was not examined histologically, the post-mortem records never name infarction, but there were three instances of aneurysm of the heart-wall, while in others the myocardium is described as 'fatty', 'friable', or 'soft and degenerate'. These descriptions are quite unreliable in lack of microscopic study.

Since the principal pathological basis is recent infarction of the heart-wall, any ante-mortem history obtained is more likely to be due to coronary occlusion than to actual rupture. In senile patients, however, cardiac infarction is usually silent or may give rise to vague symptoms only, and is quite exceptionally accompanied by severe pain, so that rupture may easily occur 'out of the blue'. This is well shown in Table IV. In cases which do not go on to rupture it is usually impossible to diagnose infarction in our patients, and the great majority of infarcts which come to *post mortem* are either undiagnosed or labelled 'heart failure of doubtful origin'.

TABLE IV.

Mode of Death in the Proved Cases of Series B.

Person's General Condition.	Sudden Death.	Short Illness. 3 Days.	Short Illness. 7 Hours.	Classical Syndrome of Infarction.	Found Dead in bed.	Severe Non-Cardiac Illness.	Totals.
Up and about.							
1 'Heart case'	—	—	—	1	—	2	3
2 Healthy	4	—	1	—	1	—	6
Bedridden.							
1 For heart	1	1	—	—	—	—	2
2 For other reasons	3	—	—	—	—	—	3
Totals	8	1	1	1	1	2	14

The many different 'exciting causes' which have been quoted somewhat lose their importance if, as we believe, the pathological basis is settled, but it is interesting to note the rarity of violent exertion—only two of Krumbhaar's own cases and none of ours—and the frequency of defaecation. The latter suggests raised blood-pressure as a factor, and the large number of deaths during sleep is not opposed to this in view of what little we know of changes in the nervous and circulatory systems in sleep.

The difficulty of separating symptoms of rupture from those of infarction invalidate any attempt to calculate the length of survival of the rupture, especially in senile and insane patients. Sudden death is common, but by no means necessarily coincides with the moment of rupture.

Site and Character of the Rupture.

The site of the tear in the early cases (Series A) is given in Table V. In cases due to infarction the site will naturally depend upon the infarcted area, and Table VI (Series B) shows this to be most commonly within the territory of the anterior descending branch of the left coronary—the vessel in which obstruction is commonest.

TABLE V.

Site of Rupture. (*Series A only.*)

Ventricle.	Ant.	Post.	Apex.	Not stated.	Totals.
Left	12	5	1	3	21
Right	4	1	—	4	9
Total	16	6	1	7	30
In two cases there was no record.					2

In the recent fourteen cases of Series B the figures are as follows:—

TABLE VI.

Number of Case.	Affected Side.	Coronary Branch.	Site of Obstruction.	Site of Infarction.	Site of Rupture.
1 (J. L. Y./45)	L	C.	¼″ from orifice	L. border, post L. wall and septum	*Ant. L. V. wall half way down
2 (J. K./46)	R	C.	1″ down	Post. R. V. wall high up	*R. border high up
3 (H. B./43)	L	M. I.	¾″ down	Lateral border L. V.	Ant. L. V. wall near lateral border
4 (R. M./38)	L	A. D.	?	Ant. wall	Ant. R. V. wall 1½″ from apex
5 (S. M./37)	L	A. D.	¾″ down	Whole L. V. wall	Ant. L. V. wall high up
6 (E. D./39)	L	A. D.	2″ down	Ant. L. V. wall	Ant. L. V. wall 1″ above apex
7 (A. W./40)	L	A. D.	1″ down	Ant. wall septum and apex	L. Ant. apex
8 (M. C./41)	R	P. D.	?	Post. wall and septum	Post R. V. wall via septum to L. V. wall
9 (A. R./35)	L	A. D.	?	Ant. wall	Ant. L. V. wall high up
10 (M. H./36)	L	C	Margo obtusa	L. border and post L. V. wall	Post L. V. wall half way down
11 (H. L./44)	L	A. D.	1″ down	Lower Ant. L. V. wall	Ant. L. V. wall 1″ above apex
12 (C. W./34)	R	P. D.	?	Post. wall	Post. L. V. wall
13 (B. M./42)	L	Twig of A. D.	Orifice	Conus arteriosus	Base of conus
14 (C. S./28)	L	?	?	Ant. L. V. wall	Ant. L. V. wall

N.B. In the cases marked ? the vessel was grossly atheromatous, but the specific obstruction causing the infarct could not be identified.

C = circumflex; A. D. = anterior descending; P. D. = posterior descending; M. 1. = first marginal branch; L. V. = left ventricle; R. V. = right ventricle.

* Partial rupture.

The size and character of the tear vary. In four of our cases it was pin-point or tiny, and in fourteen it was less than half an inch long; two were over three inches long. The tear is usually linear or ragged and is sometimes zig-zag. It may lie in any axis of the heart, but is commonly roughly vertical. Actually the size, situation, and character of the epicardial tear are alike misleading as to the respective characteristics of the rupture as a whole, for unless the tear is large, and sudden or very rapid in its formation, the blood seems to be expressed in very small quantity at each heart-beat, and may track along under the epicardium before its final exit, frequently forming an epicardial haematoma.

The occurrence and size of the haematoma will depend upon several variables, the rate of bleeding, the softness and distribution of the fat, &c., and the haematoma may be quite a distance from the rupture, as in our Case 10 (MH/36), which had a tiny tear half-way down the anterior left ventricular wall, and in which the auriculo ventricular furrow was bulging with effused blood. The final epicardial tear here was close to the myocardial rupture at a point where there was practically no epicardial fat. In such cases the final tear presumably occurs when a point is reached where a diminution in the epicardial fat or its firmer attachment to the heart-wall increases the resistance to the effusion. Some such factor may be responsible for the frequence of tears close to and parallel to a coronary vessel. This was noted in eleven of our cases, in two of which a zig-zag tear ran parallel to a tortuous coronary branch.

The course through the wall is often tortuous and hard to define in the smaller tears. The endocardial opening is usually smaller than the epicardial, sometimes markedly so. It is almost invariably hidden amongst the trabeculae at the junction of wall and septum or behind a papillary muscle. It is often difficult to find, and (even possibly shedding some light upon the rarity of incomplete ruptures) a false passage through the softened heart-wall is only too easily made at autopsy.

Microscopic appearance of the rupture. In our experience microscopic examination of the edge of the rupture gives singularly little information. The appearance varies from case to case. It may be relatively straight and clean cut, but is more often ragged and irregular, and has small patches of isolated tissue and debris along its margin. The tear may be filled with blood, or the margins lined with it, and not infrequently fibrinous deposit is formed, indicating a fair length of survival. The surrounding tissue always shows some evidence of infarction. There may be much infiltration with blood. Heavy leucocytic infiltration is in our experience part of the reaction to infarction and not an attempt to repair rupture. Krumbhaar mentions the occurrence of haemosiderin granules amongst the fibres near the edge, but we are unable to confirm this. There is usually considerable destruction of fat and infiltration with blood. The epicardium always shows some sign of reaction at and around the opening.

The tear has no discernible constancy of position relative to the infarct as a whole.

Relative frequency of rupture. It has been shown that infarction is the

commonest if not the only cause of rupture, but the converse does not hold good; on the contrary rupture is the rarest sequela of cardiac infarction. Its incidence is agreed by Benson and Hunter (5), Parkinson and Bedford (6), and Levine (7) to be about 6 per cent. In the absence of a definite clinical syndrome amongst senile dements we are unable to produce figures for comparison, but we suspect that in these persons the incidence is higher.

Age of the infarct. The age of the infarct at the time of the occurrence of rupture is hard to determine. It is impossible to date an infarct accurately by microscopy alone. In respect of the stage of reaction to the infarct it is commonest to find a well-marked line of demarcation formed, with frequently much leucocytic debris. Out of our fourteen cases histologically examined eleven were of approximately this type, three showed no line of demarcation and little change in staining reaction, whilst two showed early connective tissue in parts.

Levine, in his able monograph on infarction, throws much light on the subject. Nine of his patients died of rupture, in all of whom it had been possible to determine the onset of the infarct clinically. Of these nine, eight died within two weeks of infarction, and six between the fifth and fourteenth day. 'This,' he says, 'is the period during which necrosis is most marked and the muscle softest.' The ninth case was ruptured through an aneurysmal dilatation.

Partial rupture. Incomplete tears are very uncommon. Krumbhaar and Crowell report only three tears of the outer wall of the heart which failed to reach the endocardium. In our series we have had two such, both in men, and both confined to the superficial layers.

Case 1. (J. L. Y./45.) Male, aged 76, who had complained of abdominal pain some hours previously, died suddenly after defaecation.

Post mortem. The *pericardium* contained 12 oz. of blood and clot and its visceral layer was reddened and rough and in parts covered with firmly adherent clot. The *Heart* weighed 20 oz. and was somewhat fatty. Both coronaries were atheromatous and the left circumflex branch was completely occluded by recent clot, from the margo obtusa to within ¼ inch of its origin. The vessel was large and widely distributed, and the whole lateral area of the left ventricle and most of the posterior wall and septum were infarcted. Hidden beneath a mass of adherent clot about half-way down the left ventricle and immediately anterior to its left border was a small linear tear about ⅓ inch long and ⅛ inch deep. Careful search failed to show any internal opening.

Microscopy. Recent infarct with enormous leucocytic infiltration and much intra-mural haemorrhage. Extensive and marked pericarditis of the visceral layer. The rupture margin is covered with a thick deposit of fibrin and its opening filled with blood. The surrounding fibres are dead and infiltrated with haemorrhage, but there is relatively little leucocytic reaction near the tear.

Case 2. (J. K./46.) Male, aged 77. Known to have an enlarged heart. In bed for general condition; suddenly collapsed and died.

Post mortem. Pericardium full of adherent clot. Marked fibrinous epicarditis. Right coronary obstructed by thrombus two inches from margin. A tear high up in the posterior wall, about ¾ inch from and parallel with the occluded vessel, was quite superficial and did not communicate with the

ventricle. Diffuse haemorrhagic infiltration of whole epicardium. Large infarct of whole posterior wall and lower septum and apex.

Microscopy. Recent infarction. Muscle reduced in parts to amorphous mass. Much leucocytic infiltration, oedema, and haemorrhage.

The Mechanism of Rupture.

The actual mechanism of the tear has never been satisfactorily explained. The classical concepts are two, namely, (1) Actual bursting of the heart from the weight of the intraventricular pressure, and (2) Direct tearing of the muscle from the force of its own contraction. In comparing the action of these two on a softened area of infarction it must be remembered that the tensile pull of the contracting muscle on any unit area of the dead tissue is proved by physical calculations to be very much greater than the outward thrust of the intracardiac pressure.

In hearts containing infarctions the factors which weaken the wall locally are softening and haemorrhage. The importance of softening is very great and is seen firstly in the coincidence emphasized by Levine, of rupture with the time when softening is maximal, and secondly in the almost invariable association of rupture with excessive mural fat, to which several observers have called attention and which this series confirms. Speaking generally, superficial infarction of the epicardial fat is exceedingly rare, the anastomoses of the arterial telae adiposae affording ample protection, as Campbell (8) points out. When fatty deposition is excessive, however, this protection is obviously diminished in direct ratio to the degree of the fatty increase. In such cases not only are the deeper layers of the fat liable to infarction but there is frequently an accompanying diffuse fatty infiltration of the whole of the heart, which in some of our cases has proceeded to an astounding degree. Fat necrosis, as is well known, proceeds almost to liquefaction, so that when infarction occurs in such a heart not only is the resistance to strain either of muscular force or of haemorrhage greatly diminished, but any haemorrhage, once initiated, is practically led into the epicardium.

Haemorrhage is an important factor. It is commonly accepted that the haemopericardium which is found in nearly all cases must come from the ventricle, but closer examination renders this less certain. Haemopericardium occurs in cases of partial rupture with no communication with the ventricle (Cases 1 (J. L. Y./45), 2 (J. K./46)) or even in cases of haemorrhagic infarction with no visible rupture of any kind. In such cases the blood must come from the heart-wall, and in our view such intramural haemorrhage may be not only a result but a factor, and sometimes the main factor, in the causation of cardiac rupture.

Such haemorrhage commonly occurs as capillary haemorrhage from the hyperaemic area at the edge of a recent infarct, and is responsible for the 'apoplectic' infarcts which are not infrequently seen; indeed all infarcts pass through a haemorrhagic stage the intensity of which must vary with such factors as the degree of softening and the time of its occurrence. From gross

apoplectic infarction to actual rupture of the heart is a short step, especially in the presence of semi-liquid necrotic fat. So much for haemorrhage from the wall. Its importance in any given case is difficult to evaluate, though one cannot doubt that it frequently plays a part and sometimes the deciding part.

The part played by muscular action must now be considered. It is plain that local muscular contraction is not concerned, for the local muscle is dead and inactive. An important part appears to be played, however, by the effect upon the dead area of the contraction of the heart as a whole, and much light is thrown upon the subject by the site of the internal opening of the tear. In the majority of cases this is placed either at the base of a papillary muscle or at the junction of the septum and the outer heart-wall—both points subjected to the stress of the divergent action of two main muscle masses. The subendocardial fibres though not always necrotic are usually affected to some extent, as is shown by microscopy and by the frequency with which mural thrombi form *in vivo*. Subjected as they are to heavy stress, weakened from ischaemia, and having behind them an infarcted area softened, or it may be suddenly tense from intramural effusion, these may give way, and though the initial opening may be very small each subsequent systole will tend to separate its edges.

For the deeper layers of the myocardium the effect of muscular contraction is not so easily seen, and its importance is probably limited. Were it the main factor, the tears should follow a fairly constant course from within out, which is definitely not the case. Again, rupture should be commonest in well-muscled hearts instead of occurring, as it almost invariably does, in fatty and poorly-muscled ones, whilst in our experience large infarcts *without* rupture occur mainly in the heavily-muscled type. Lastly, the tortuous course of the tear and the often extensive tracking of blood into the surrounding fatty tissue suggest that haemorrhage, whether from wall or ventricle, is the direct cause of most ruptures, and that the muscular force instead of 'tearing the heart' acts mainly indirectly by supplying motive power to the destroying blood.

The Mechanism of Death.

Quite obviously the myocardial tear in itself is not fatal, and theoretically death should occur from obstruction of the great veins by the raised intra-pericardial pressure. In some cases, however, there is little blood in the pericardium, whilst the sudden deaths suggest ventricular fibrillation and similar disasters. The danger of a haemopericardium, however, depends greatly upon the speed with which it is produced, whilst that sudden death can occur from venous obstruction is proved by a case which is we think unique.

Case 3. (H. B./43.) Female, aged 80, previously well, was found dead in a lavatory, having evidently died in the act of defaecation.

Post mortem. Pericardium contained 7 oz. of blood. *Heart*, weight 11½ oz. Marked increase in epicardial fat and fatty infiltration of the whole heart-wall. Coronary atheroma severe. The left coronary immediately after its origin trifurcated into anterior descending circumflex, and a large marginal

branch. The last was completely obstructed by athero-thrombosis about ¾ inch from its origin.

The left border of the left ventricle was infarcted and there was a zig-zag rupture ½ inch long with its lower limit ¾ inch above the apex.

The left auricular appendage was completely inverted, its apex lying within the mitral valve orifice.

Microscopy. Infarct. Fibres swollen and oedematous: much leucocytic infiltration; marked haemorrhagic infiltration, especially near rupture line. In one part *young* connective tissue was seen.

Comment. The inversion must obviously have occurred very shortly before death as there was no reaction suggesting constriction around its base. A conceivable explanation is that the haemopericardium though small was sufficient to obstruct the pulmonary veins and that a potential vacuum was set up by the 'diastolic suck'. Presumably the sac filled very rapidly.

Summary.

1. Forty-six cases of spontaneous cardiac rupture are reviewed and discussed. Recent acute infarction of the heart is considered to be almost invariably the underlying cause.

2. The association of rupture with senility and mental disease is noted.

3. The mechanism of rupture is discussed and the importance of excessive fat, of softening, and of haemorrhage as factors, is emphasized.

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DESCRIPTION OF PLATES.

1. PLATE 4, Fig. 1. *Case* 7 (AW/40). Cross-section showing course of tear and epicardial haematoma.

2. PLATE 5, Fig. 2. *Case* 11 (HL/44). Showing fatty heart, zig-zag tear, and apical haematoma.

3. PLATE 5, Fig. 3. *Case* 3 (HB/43). Showing (*a*) inversion of auricular appendage, (*b*) athero-thrombotic obstruction, (*c*) rupture.

4. PLATE 6, Fig. 4. Same case from within, showing (*a*) the inverted appendage.

5. PLATE 6, Fig. 5. *Case* 2 (JK/46). Showing (*a*) clot in right coronary artery, and (*b*) partial rupture close and parallel to vessel.

Appendix.

Case Reports of Series B.

Case 1. (J. L. Y./45.) Reported in detail in text.

Case 2. (J. K./46.) Reported in detail in text.

Case 3. (H. B./43.) Reported in detail in text.

Case 4. (R. M./38.) Female aged 80. Bedridden. For several months had dyspnoea on slight exertion and occasionally in paroxysms without exertion. No heart signs. Developed a febrile illness diagnosed as 'influenza' and died unexpectedly three days later.

Post mortem. Pericardium contained 4 oz. of blood. *Heart* weighed 18½ oz. Coronaries grossly diseased; no obstruction defined. A ragged linear tear one-third of an inch long immediately to the right of, and parallel with, the anterior descending branch. This ran upwards to its inner opening in the right ventricle close to the septum. Epicardial fat very excessive and much infiltrated with blood. Muscle very soft and fatty '? infarct'.

Microscopy. Infarct not well demarcated. Little leucocyte infiltration. Marked diminution of nuclei with some swelling of muscle fibres, oedema, and minute haemorrhages. Rupture line not sectioned.

Case 5. (S. M./37.) Male aged 65. Known to have an enlarged heart. Died of lobar pneumonia with pleural effusion on the (?) eighth day.

Post mortem. Pericardium contained 8 oz. blood and clot. *Heart* weight 16 oz. Fatty. Coronaries atheromatous. Left anterior descending branch obstructed by athero-thrombotic mass three-quarters of an inch from its orifice. A ragged tear half an inch long, a little below the obstruction and near the left border of the heart. Whole anterior wall except the apex and almost the whole septum involved in a recent infarct.

Microscopy. Infarct well demarcated with muscle-change varying from diminution of nuclei to complete destruction, the centre being quite amorphous. Whole area heavily infiltrated with leucocytes. Marked epicardial and endocardial reaction. *Rupture* fairly clean cut with gross haemorrhage in surrounding tissues, especially in the epicardial fat.

Case 6. (E. D./39.) Female aged 79. Bedridden, restless, and demented. Not suspected of cardiac disease. Collapsed in bed and died in a few minutes.

Post mortem. Pericardium contained over a pint of blood and clot. *Heart* weight 11½ oz. Very fatty. Coronaries grossly diseased and calcified at flexures. Left anterior descending branch completely obstructed about two inches from its orifice. A linear tear half an inch long close to the artery near the apex.

Microscopy. Infarct not well demarcated. Early leucocyte infiltration. Tissue changes range from diminution of nuclei to swelling and disintegration of fibres. Marked epicardial reaction. *Rupture* (serial sections) very irregular course. Endocardial opening small; endocardium stripped away from wall by blood. Margins of tears lined with clot. Much infiltration of surrounding tissues with blood, especially in the epicardial fat.

Case 7. (A. W./40.) Female aged 73. Bedridden, suffering from aortic incompetence with gross cardiac enlargement. Sudden dyspnoeic attack—died in five minutes.

Post mortem. Pericardium contained 16 oz. blood and clot. *Heart* weight 21 oz. Epicardial haematoma at apex. A tiny tear at its left border just above apex. Coronary disease marked. Left anterior descending branch blocked by

clot one inch from its orifice. An aneurysmal dilatation the size of a gooseberry at the apex, its wall only one-eighth of an inch thick. Close to its edge was the rupture line.

Microscopy. A recent area of necrosis at the edge of the aneurysm. Not sharply demarcated. Extensive tissue death with leucocyte infiltration and in parts young connective tissue. Rupture line not well shown.

Case 8. (M. C./41.) Female aged 87. Slow cardiac failure with gross enlargement. Classical syndrome of infarction for eleven days before death.

Post mortem. Pericardium contained 5 oz. of blood. *Heart* weight 16½ oz. Very excessive fat. Large subepicardial haematoma over posterior wall near apex. Small irregular tear one-third of an inch long at base of one bulla, running across the septum to the right ventricle at the septomural junction. The right coronary was almost completely obstructed from its orifice and its lumen could not be traced. A large recent infarct in the posterior wall and septum.

Microscopy. 'Recent Infarct.' (No further record now available.)

Case 9. (A. R./35.) Female aged 72. Previously healthy. Found dead in bed.

Post mortem. Pericardium contained 3 oz. of clot. *Heart* weight 8½ oz. Very fatty. A linear tear half an inch long high up on anterior wall of left ventricle. Gross coronary disease; no obstruction defined.

Microscopy. Infarct. Commencing demarcation and some leucocyte infiltration at the edges. The fibres here are swollen with some loss of nuclei. In the centre is a mass of dead fibres, leucocytes, and débris. Marked pericardial and endocardial reaction. Rupture has ragged edges and the whole surrounding area is ploughed up by blood.

Case 10. (M. H./36.) Female aged 75. Previously healthy, suddenly collapsed and died.

Post mortem. Pericardium contained 1 pint of blood and clot. *Heart* weight 13 oz. Gross coronary disease. Left circumflex obstructed by atherothrombotic mass at the margo obtusa. Half-way down posterior wall a tiny tear filled with clot, running a tortuous course to its inner opening at the base of the left posterior papillary.

Microscopy. Infarct strongly demarcated. Heavy leucocyte infiltration. Muscle-fibres swollen and structureless, with much debris in their interstices. Rupture very near edge of infarct; a widely gaping tear with ragged edges lined with fibrinous deposits. Some haemorrhagic infiltration of the neighbourhood. Marked epicardial reaction.

Case 11. (H. L./44.) Female aged 75. Feeble, bedridden patient not suspected of cardiac disease. Was sitting up in bed when she fell back dead.

Post mortem. Pericardium contained 12 oz. of blood and clot. *Heart* very fatty. Anterior descending branch obstructed one inch from orifice. A zig-zag tear about one inch long and roughly parallel to the tortuous coronary vessel about one inch above the apex. Inner opening behind anterior papillary bundle.

Microscopy. Infarct with early leucocyte reaction and swelling of fibres with increase in staining and loss of nuclei. The whole area was ploughed up and destroyed by haemorrhage and the rupture line was not well distinguished.

Case 12. (C. W./34.) Female aged 76. Not suspected of cardiac disease. Died suddenly.

Post mortem. Pericardium contained 3 oz. of blood. *Heart* weight 8½ oz. Linear tear three-quarters of an inch long close to and parallel with posterior descending branch about half-way down. Inner opening behind left posterior

papillary. Lumen of right coronary could not be traced; gross atheroma. Muscle yellow and mottled, very fatty. Infarct not definable.

Microscopy. Infarct well demarcated. Nuclear diminution and swelling of fibres with oedema and some tiny haemorrhages. Rupture not cut.

Case 13. (B. M./42.) Female aged 95. Had an enlarged heart with an early diastolic murmur at the apex during at least two years. No signs of failure. Collapsed whilst dressing and developed right-sided hemiplegia with deepening coma until death three days later.

Post mortem showed thrombosis of the left anterior cerebral artery and softening in its whole distribution. Pericardium contained very little altered blood. A single old adhesion between its layers just above and posterior to the apex. *Heart* weight 4 oz. Enormously fatty. Linear horizontal tear one and a quarter inches long at base of conus arteriosus. The right ventricular wall was almost entirely fat.

Microscopy. Infarct surrounding rupture with very early staining changes and nuclear loss and a little infiltration with blood. Leucocyte reaction in epicardium. An old infarct below the adhesion lower down.

Case 14. (C. S./28.) Female aged 74. Extreme arteriosclerosis; otherwise in good health. Found dead in chair.

Post mortem. Pericardium full of clot and serum. *Heart* weight 12 oz. Severe coronary atheroma. Rupture one inch long adjacent to anterior descending branch. Tortuous course into left ventricle. Muscle showed advanced fatty infiltration. (? Infarct.)

Microscopy. Recent infarct with swelling and oedema, marked leucocyte infiltration and much haemorrhage, especially in epicardiac fat. Marked epicardial reaction.

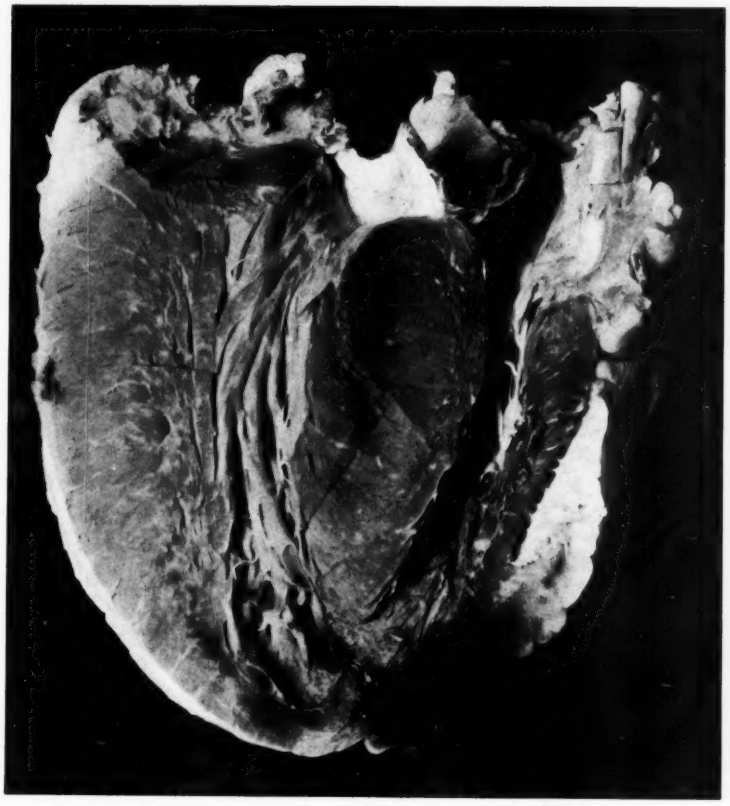

FIG. 1

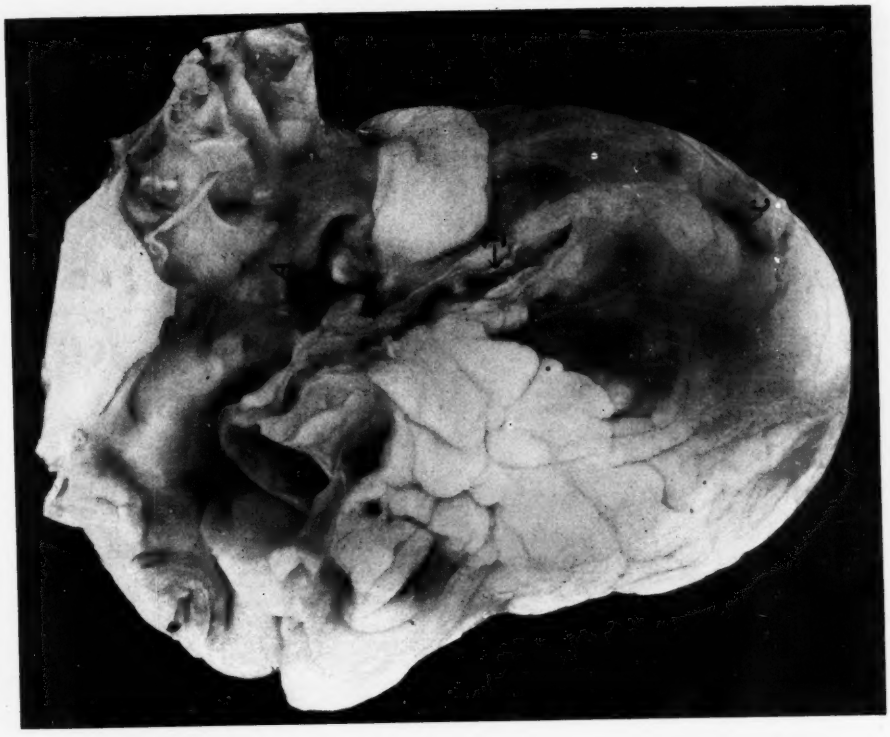

FIG. 3

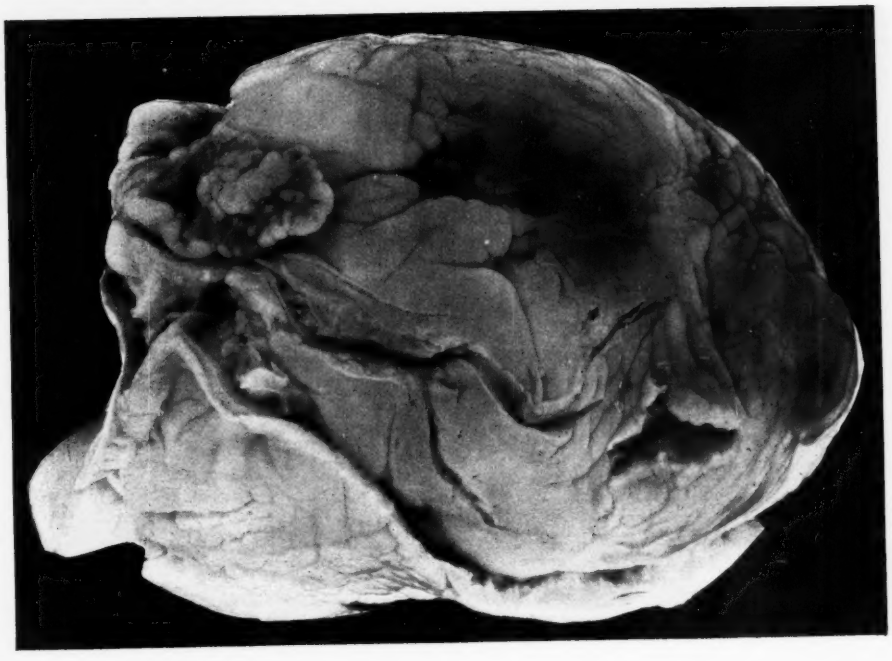

FIG. 2

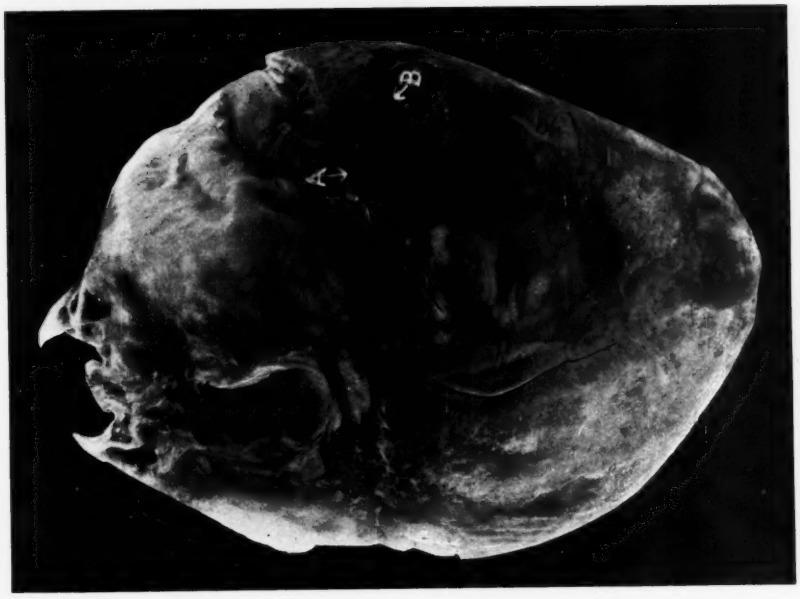

FIG. 5

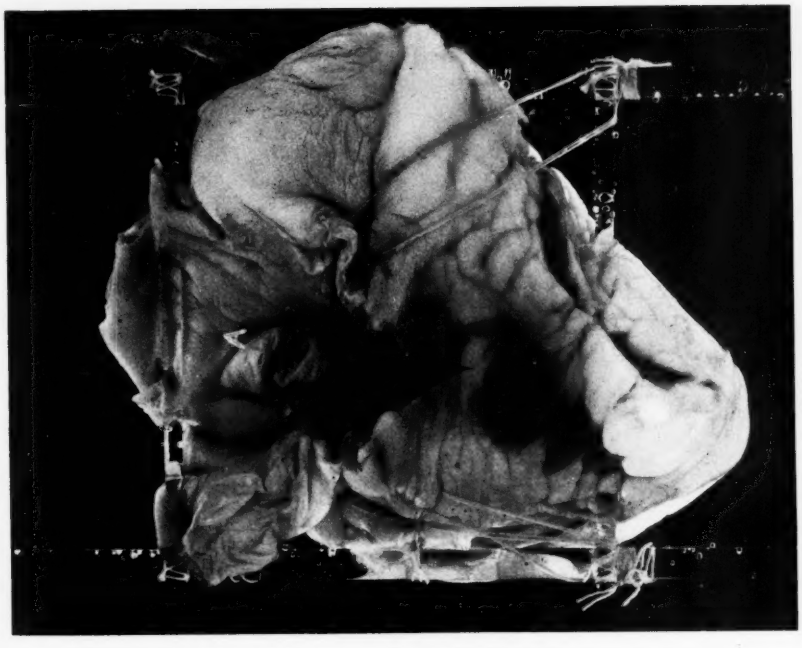

FIG. 4

616.12–008.311

PAROXYSMAL AURICULAR FIBRILLATION[1]

A RECORD OF TWO HUNDRED PATIENTS

By JOHN PARKINSON and MAURICE CAMPBELL

I. *Introductory.*

Auricular fibrillation often occurs in paroxysms, though the established form is more familiar. This paper is based on the notes of two hundred patients who have had such paroxysms. We wish to consolidate opinion on a significant and serious form of palpitation, to consider its cause, and to describe its development and prognosis. Paroxysmal fibrillation will be found most often in those with other evidence of heart disease; and then it commonly rules the clinical picture, determining the further course of the malady and its treatment.

Many of these two hundred patients have been seen from time to time over several years, and with a disease of this nature one can get little idea of its evolution without such prolonged observation. Generally orthodiagrams have been obtained as well as electrocardiograms, for radioscopy may show the presence of heart disease when other evidence is inconclusive, as, for example, when the aorta is widened or lengthened. Special attention was not paid to the details of the electrocardiograms; though there were several patients in all the groups with normal electrocardiograms (apart from fibrillation) this was a common finding only in those who had no other signs of heart disease. As would be expected, there was more often preponderance of the right ventricle in those with mitral stenosis, and of the left ventricle in those with high blood-pressure and myocardial disease. The onset and offset are so seldom recorded that we furnish examples in Fig. 1 (see also Fig. 119 (40)). Fig. 2 merely shows typical electrocardiograms in and out of a paroxysm, the ventricular complexes being similar despite the change of rhythm.

Theoretically, there should be two cardiograms in each case, the first one showing fibrillation and the second normal rhythm, a condition which was fulfilled in 113 of these 200 patients (in 87 by electrocardiograms and in 26 by polygrams). In 17 others fibrillation was already established, but there was a clear history of previous paroxysms; and in another 9 the clinical diagnosis was confirmed later when fibrillation became established. These 139, in whom the diagnosis was conclusive, formed more than two-thirds of the total. In the remaining 61, whose history only was available, nearly all had

[1] Received August 26, 1930.

been seen during the attack by a doctor who was conversant with fibrillation. In three such patients electrocardiograms of attacks have been obtained since this paper was first written and have confirmed the clinical diagnosis. The greatest care was taken not to include mere nervous palpitation, and if there were

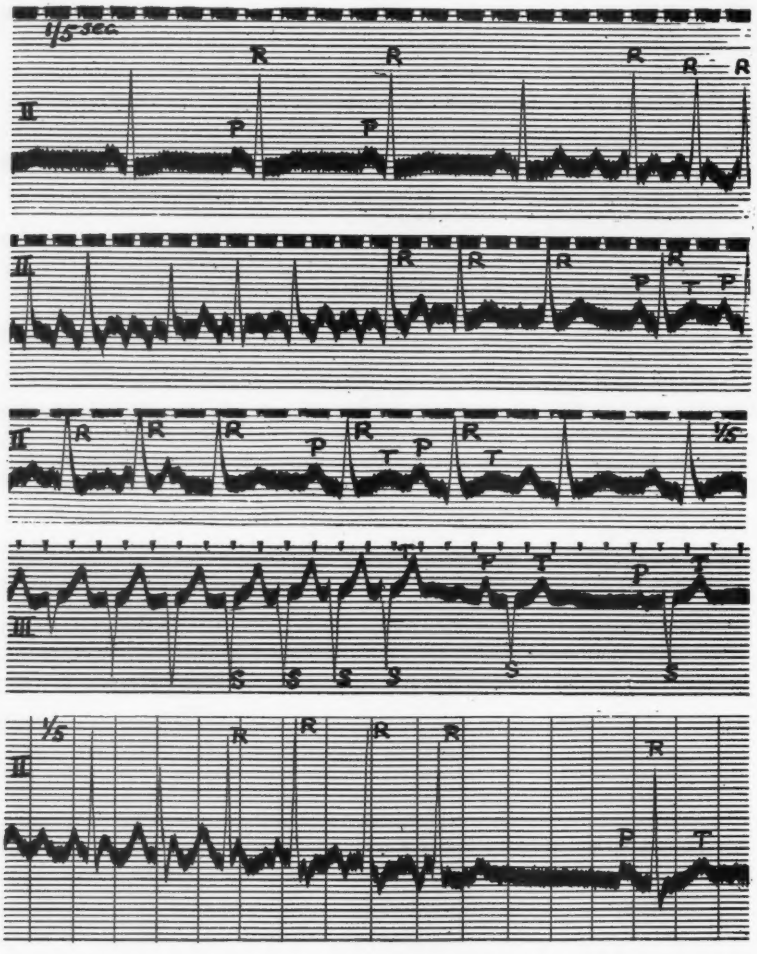

FIG. 1. Electrocardiograms illustrating (*a*) the onset (*b–e*) the offset of paroxysms of fibrillation. (*a*) from Case 108, (*b*) and (*c*) from Case 150, (*d*) from Case 9, (*e*) from Case 181.

mistakes they would be too few seriously to invalidate the following statistics. More than half of these patients were seen in private practice, and the rest in a general or a special hospital. Reference to twenty of them has already been made in our paper on quinidine treatment (87).

Before auricular fibrillation was clearly distinguished, paroxysmal fibrillation might readily have been confused with paroxysmal tachycardia; but in early classical papers dealing with this disorder (Cotton (13), Bouveret (3), and Her-

ringham (45)) we have found no evidence that it was. A probable example ot paroxysmal fibrillation was described by Nothnagel as early as 1876 (83). In 1901, A. Hoffmann (47) observed eight patients in whom there had been rapid action of the heart with sudden onset and offset, like paroxysmal tachycardia, except that the pulse was completely irregular, and two years later Merklen (79) gave an excellent account of the condition.

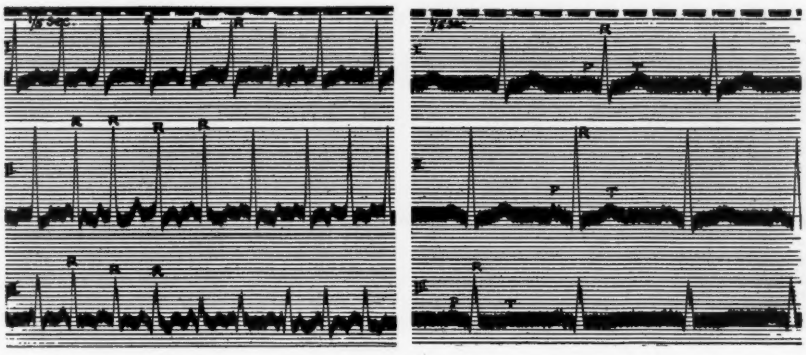

FIG. 2. Electrocardiogram (*a*) during and (*b*) after the offset of a paroxysm of auricular fibrillation (Case 108).

Mackenzie's *Study of the Pulse* (1902) and his papers on 'The Inception of the Heart Rhythm by the Ventricle' (1904) and 'The Interpretation of Pulsations in the Jugular Vein' (1907), (70, 71, 72), were differentiating clearly sinus arrhythmia, extra-systoles, and auricular fibrillation, though this name was not then used. Of the last he says, 'It is generally permanent when it once appears but may be paroxysmal', and he gives polygraphic tracings of a patient who had such attacks, their duration varying from five hours to eleven days (70).

Cushny was first responsible for the view that fibrillation of the auricles, already known in the physiological laboratory, was of clinical importance. Later, in 1907, he and Edmunds (15) described a patient with paroxysmal irregularity of the heart, and suggested it was due to fibrillation; tracings of her arterial pulse, which were taken in 1901 after an operation, confirm their diagnosis. She continued to have paroxysms for eight years until fibrillation became permanent.

In 1907 Hornung published three 'Atypical cases of paroxysmal tachycardia', which the tracings show to have been fibrillation (49). In the following year Müller (81), Hewlett (46), Bard (1), and Mackenzie (74) gave clear clinical pictures; Mackenzie's of a lady whose pulse one night was so rapid and irregular that every one expected her to die, but the next morning was normal, and she was almost well.

Although several of these papers are now convincing, especially that of Cushny and Edmunds, it was not until the electrocardiographic proof of

auricular fibrillation by Rothberger and Winterberg (93) and by Lewis (67), both in 1909, that it became widely recognized. Lewis's second paper (68) was so complete in its scientific proof and clinical descriptions that the condition became generally known. He mentioned five cases where fibrillation was paroxysmal, and the same year Fox (31) wrote on the significance of transitory delirium cordis.

After that many other cases were described, and in 1914 Heitz added eight of his own and gave an excellent study of the whole subject (44). It will be more convenient to refer to subsequent papers as the points with which they deal come to be considered with our own series: general reviews have been published by Carpentier (7), Mason (78), Stayitch (101), and Patterson (88).

II. *Aetiology.*

A question of interest is whether paroxysmal fibrillation is compatible with a healthy heart or whether its very occurrence is evidence of disease. Gossage and Hicks (36) advanced the view that fibrillation may be caused by toxic or reflex influences on a slightly affected, or even on a healthy heart, as well as by structural heart disease. Recently Cowan (14) has revived and elaborated this, suggesting that when established it is generally caused by organic disease, but when paroxysmal more often by toxic or reflex factors. This is an interesting distinction which cannot be accepted without reserve, because paroxysmal fibrillation so often becomes established later and because most patients with paroxysms already have structural disease. The distinction is valid in the sense that there must be some chemical or reflex stimulus which provokes a paroxysm, whether the heart itself is healthy or diseased. Table I shows the aetiology of our two hundred cases.

TABLE I.

Aetiology of our 200 Cases of Paroxysmal Auricular Fibrillation.

	Men.	Women.	Percentage of total cases.
Rheumatic heart disease	17	27	22
Syphilitic aortitis (with or without aortic incompetence)	5	0	2·5
Hyperpiesis (systolic B.P. above 160 *and* diastolic above 100)	32	16	24
Myocardial disease (coronary atheroma, &c.)	32	13	22·5
Goitre	7	21	14
No evident heart disease:			
(*a*) infective or toxic causes	10	2	6
(*b*) no apparent cause	15	3	9
Total	118	82	

(1) *Rheumatic heart disease.* This was present in 22 per cent.—Cases 1–44—a smaller proportion than in a corresponding group with established fibrillation (6). There were thirty-eight with valvular disease, nearly always mitral stenosis with or without aortic incompetence. There were also sixteen with a history of rheumatic fever, but no valvular disease; in six of these no other abnormality was found, and they have, therefore, been included as rheumatic;

but in the other ten, who were considerably older, there was arteriosclerosis or hyperpiesis, so that they have been included according to these findings, the rheumatic history being neglected.

(2) *Syphilis.* There were 2·5 per cent. with evidence of syphilis—Cases 45–49. In none were there typical recurrent paroxysms such as were present in the others, so that syphilis appears to be no more important as a cause of paroxysmal than of established fibrillation. All were men, mostly aged 40–50; three had aortic incompetence.

(3) *High blood-pressure.* This was found more frequently than in a corresponding group with established fibrillation (6), for it was present in 24 per cent.—Cases 50–97. They were first divided into two grades—(*a*) systolic B.P. above 180, or diastolic B. P. above 120, and (*b*) systolic B. P. above 160, and diastolic B. P. above 100; but as there did not appear to be any useful distinction the two groups were taken together. There were about equal numbers in each, and the average blood-pressure was 195 systolic, 115 diastolic.

(4) *Myocardial disease.* This was present in 22·5 per cent.—Cases 98–142. There were thirty-one with evidence of arterial disease, apart from those included in other groups. Sometimes the peripheral arteries were thickened, sometimes the aorta was found to be enlarged on X-ray examination, sometimes there were changes in the retinal arteries, and often the blood-pressure was at the higher limits of normal as well. Coronary thrombosis and angina, though rarely present, were taken as evidence of coronary disease. There were fourteen others without arterial disease, as above defined, who had gross enlargement of the heart or signs of congestive failure. As they did not differ greatly from those with arterial disease, both have been considered together.

(5) *Goitre.* This was responsible for 14 per cent.—Cases 143–70. Exophthalmic goitre, past or present, was found in seventeen; and eleven had a simple goitre or an adenoma of the thyroid, sometimes with obvious hyperthyroidism, but often with a long-standing goitre and no obvious hyperthyroidism; three had also high blood-pressure. The proportion with goitre will of course vary greatly with the locality and with the type of cases at the observer's disposal. Undoubtedly the thyroid may be responsible for fibrillation where there is little increase in the metabolic rate, and so the possibility of latent hyperthyroidism should never be forgotten, a point which has already been emphasized (22, 66, 108).

(6) *No heart disease.* There were 15 per cent. where, apart from the paroxysms, no evidence of heart disease could be found—Cases 171–200. It is unlikely that all these had normal hearts, for some of the older ones especially were very ill, and complete examination, e. g., by X-rays, could not be made. In twelve, who will be discussed later with similar reported cases, the attacks were apparently associated with septic or toxic factors; in eighteen there was no apparent cause, and often the patient has remained well for years and free from any abnormal signs except for frequent or occasional attacks.

These conclusions about the aetiology are borne out by a review of the

literature. Table II has been compiled from some published series of cases—(26, 31, 44, 54, 63, 77, 78, 88, 98), excluding certain papers dealing with goitre only (39 cases)—(21, 51, 53). Nor does it include accounts of one or two cases only, probably reported because they were thought to be unusual; often these were of special interest, so that they are more fully discussed in the section on toxic and infective factors.

TABLE II.

Aetiology of 122 Cases collected from the Literature.

	Percentage of cases.
Rheumatic heart disease	20
Hyperpiesis	15
Myocardial disease or arteriosclerosis (without high blood-pressure)	23
Goitre	12
No evident heart disease:	
(*a*) infective causes 11 (pneumonia 5, severe sepsis 3, plural effusion 2, influenza 1); toxic causes 14 (digitalis therapy 4, alcoholism 4, tobacco 3, post-operative 3)	20
(*b*) no apparent cause	10

Toxic and infective causes. Pneumonia is sometimes the cause of paroxysms, and Cohn (11) observed them in twelve out of 123 patients (seven of whom were not having digitalis), though this proportion must have been unusually high. We have seen such attacks in four patients; in the first the only attack was associated with pneumonia (Case 200[2]), but in the second, who had mitral stenosis, fibrillation became established some years later (Case 6), and in the two others attacks had occurred apart from it and only increased in frequency with it. Yet another case with frequent attacks was free when she had pneumonia. Paroxysms with or just after pneumonia have often been reported (26, 40, 54, 68, 76, 78, 94, 100). Somewhat similar was the occurrence of paroxysms in two of our patients when they had pleural effusions due to thoracic neoplasms, and Dr. R. A. Rowlands tells us that he has seen them more than once with cancer of the lung; they have also been recorded with simple pleural effusions (78, 96).

Rheumatic fever occasionally causes attacks (54, 68, 77) (Cases 28 and 44); Floystrup (30) has noted them with pericarditis. Established fibrillation is uncommon with infective endocarditis, so that it is interesting to find this present in two of our cases and in two of Lewis (68) and of Mason (78). A patient originally reported as having temporary fibrillation in infective endocarditis had really a septic nephritis with multiple thrombosis, from which he made a good recovery (18). Cases have been reported in septicaemia (26), in tonsilitis (54), in facial erysipelas (34), in influenza (88), after diphtheria (88), with amoebic dysentery (61), and in an old man with osteomyelitis (Case 195). Borg (2) has recorded paroxysms in diabetic coma. One of our cases had his first attack with dysentery (37), and another with an amoebic liver abscess, but

[2] Notes of most cases referred to in the text by numbers without other details are given in the appendix; but even short notes of the whole two hundred would occupy too much space.

the after-history shows that other factors were involved. Case 24 is recorded in the appendix. Case 87 suffered from hemiplegia in 1918 when he was 32. No cause was found; the Wassermann reaction was negative, and he made a complete recovery in four days. In 1919 he had malignant malaria followed by an amoebic abscess of the liver; and at this time appeared his first paroxysm of fibrillation, which lasted six hours. He was quite well till 1926, when a second paroxysm started without apparent cause and lasted 24 hours. He was seen again in 1930, and was having about three attacks a year, each lasting 12–24 hours; intervally his health was good. He had increased in weight, the electrocardiogram was normal, the blood-pressure was 180/105, and X-ray showed slight enlargement of the heart and a small increase in the aortic shadow.

Felberbaum and Finesilver (29) saw attacks in three cases with the pyrexia following a few days after biliary colic. They and Wolferth (109) also have described single paroxysms with acute appendicitis, and we have seen a similar one, and another following gastro-enteritis (Case 192).

In our experience cystitis and pyelitis following on an enlarged prostate are not uncommon causes of these paroxysms, as well as of frequent extrasystoles. But on the whole the shortness of these lists shows that an acute infection is only an occasional factor in the aetiology.

Patients with complete heart-block, constant or intermittent, and paroxysms of fibrillation have been reported (28, 95, 107); but it is relatively uncommon for these two conditions to occur together. Recently we have seen a woman of 60 in an isolated paroxysm of fibrillation with a slow ventricular rate of 56; this was followed within two or three days by normal auricular rhythm with 2 : 1 heart-block: it was thought to be due to coronary occlusion. The unique combination of paroxysmal fibrillation and congenital heart disease is reported by Semerau (96); the paroxysm was recorded graphically following a pulmonary infarction, and necropsy showed a defect of the auricular septum.

The production of paroxysms by drugs and chemical agents must be considered next. The action of digitalis in starting fibrillation is well proven, and was emphasized in an early paper by Mackenzie (73). We have two such examples, but have been more impressed by the frequency with which fibrillation has stopped while the patient was taking digitalis. This question will be discussed in the section on treatment.

No other drug appears to have produced fibrillation so frequently, though it has been described after adrenalin (50, 99), arsenic (8), aspirin (39, 44), carbon monoxide (12), and hydrogen sulphide (92). Some of these have not been followed long enough to be sure that other attacks did not occur without obvious cause, though certainly those observed were determined by these agents. Edens (24) states that in seven of his cases fibrillation was due to improper treatment of goitre with iodine.

The influence of tobacco and alcohol is difficult to estimate. They are often used excessively by patients with paroxysmal fibrillation, but there are

few reports of complete relief for any long period with abstinence from either, to prove them as more than accessory factors. Alcohol has been blamed as the basis of such attacks in some cases (23, 44, 46, 68), as have also tobacco (44, 56, 88), and coffee (81). In relatively few of our patients could the attacks be entirely or even partly attributed to these causes.

Paroxysms are liable to occur in patients with goitre just after thyroidectomy (20, 25, 97), as they did in two of our cases. This may be partly due to an acute hyperthyroidism, but they occur after other operations. In Case 197 fibrillation started (so far as is known for the first time) when he was given chloroform and ether for an operation for hernia; this was postponed, and the attack stopped after six hours. Nothing abnormal could be found on examination. After a short holiday he was again anaesthetized, and fibrillation started as before after a few minutes; but the operation was continued without any difficulty, and normal rhythm returned after half an hour before he had completely recovered consciousness. Similar paroxysms have been described (64, 100).

Isolated cases have been reported where attacks were apparently induced by vagal pressure (91), by deep breathing (98), by coughing (24), and by straining at stool (49). Electric shocks also have been accounted the responsible factors (25, 42, 59, 91).

It is difficult to establish the relation between indigestion and paroxysms. Dietary indiscretions and over-eating have often been blamed (24, 44, 81); and Cowan (14) has assembled some good examples of paroxysms due to indigestion and to various intoxications, but they are interesting rather than representative. Many patients are inclined to attribute their attacks to such causes, though generally the evidence is not convincing. Often the abdominal discomfort induced by the attack is regarded as the cause; yet with an ulcer or carcinoma of the stomach, where flatulence and dyspepsia are striking symptoms, paroxysms rarely occur.

Taking our cases as a whole, there were 39 where some toxic or infective agent seemed of importance. In 12 there was no evidence of heart disease apart from the paroxysms, and in the remaining 27 there was other evidence. The following seemed causal or contributory factors: pneumonia 4, pleural effusions 2, and influenza 2; infections, mainly urinary and abdominal 12; operations 2, and anaesthetic 1; digitalis 3, tobacco 6, and alcohol 7.

Having reviewed the various causes of these paroxysms, we end this section with the opening question—Can they occur in a patient with an absolutely healthy heart? We believe they can, though it is exceptional.

There are several accounts where toxic and infective agents were held to be entirely responsible and the heart appeared normal. Thus Marvin and White (77) mention a case they followed carefully for six years; Edens (24) another where the first attack occurred after a bomb explosion and subsequent ones on excitement; Mackenzie (76) another where effort induced an attack lasting two hours, after which the patient remained free for ten years; Wencke-

bach (106) has also emphasized this. In Mouquin's patient (80) the first attack followed his father's death, yet the heart was healthy enough for him to be alive forty years later, and Robinson (92) could find nothing abnormal at necropsy in one young man who had been subject to paroxysms. Our Cases 174, 186, and 191 are of interest in this connexion. De Boer (17) has discussed the mechanism by which it is possible for reflex influences to initiate fibrillation.

In 85 per cent. of our cases there were other signs of heart disease. In the remaining 15 per cent. the heart appeared to be normal except for the occasional attack, and in some there was very good evidence that it was so. But if there have been more than two or three attacks, it is improbable that the heart is healthy and that minor toxic or infective agents are entirely responsible. It would seem only reasonable that some disease of the heart, however slight, must as a rule predispose it to such a disorder of rhythm; and that such commonplace and widespread agents are no more than contributory causes.

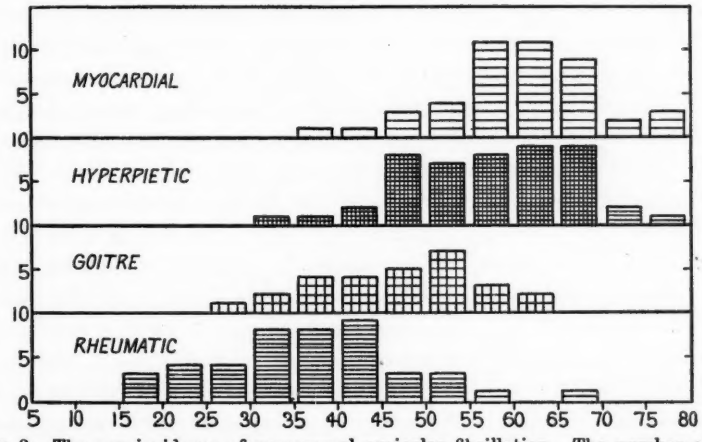

FIG 3. The age incidence of paroxysmal auricular fibrillation. The number of cases in each five-year period are shown for the four main aetiological groups separately; from below upwards—rheumatic heart disease, goitre, hyperpiesis, and myocardial disease.

TABLE III.

Age Incidence at Onset of Paroxysms.

Aetiology.	Average age.	to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 to 64	65 to 69	70 to 74	75 to	Total.
Rheumatic	35	3	4	4	*8*	*8*	*2*	3	3	1	0	1	—	—	44
Hyperpietic	57	—	—	—	1	1	2	*8*	*7*	*8*	*9*	*9*	2	1	48
Myocardial	61	—	—	—	—	1	1	3	4	*11*	*11*	*9*	2	3	45
Thyroid	47	—	—	1	2	4	4	*5*	*7*	3	2	—	—	—	28
Unclassified or without heart disease	45	—	3	2	4	3	5	4	4	3	5	1	1	—	35
All cases	50	3	7	7	15	71	21	23	25	26	27	20	5	4	200

Age and sex incidence. On the whole, there were more men than women in each group, except those with rheumatism and goitre. The rheumatic were the youngest, mostly 25–45; next came the thyroid cases, mostly 40–55; next

the hyperpietic, mostly 45–70; and finally the myocardial, who were mostly 55–70. There seemed to be no special age incidence among those without other evidence of heart disease (see Fig. 3 and Table III). Fibrillation, it is generally agreed, is rare in children, and recently Cookson (11) found that no more than 2·5 per cent. of a thousand patients with fibrillation were under 18; in only two of these was it paroxysmal. Neuhof (82) has published a record of a short attack in a child of eight.

III. *Symptomatology. The Duration of Paroxysms and their Classification.*

Palpitation was the symptom most often noted during an attack, yet few of the patients who complain of palpitation have paroxysmal fibrillation. It may be a larger proportion than is supposed, for among these 200 there were 20 doctors, and it is specially with them that conditions are favourable for identifying brief paroxysms, though in fact many intelligent patients are themselves aware of the rapid irregular pulse and can accurately describe the attacks.[3]

The symptoms were very variable in severity. A few patients were unaware of attacks which were registered; as they generally had some limitation of effort between times the added check escaped their notice. Others became dangerously ill even with short attacks, though some of these were quite well between.

In health a paroxysm may come as a great shock. Thus Case 199, returning as fit as ever from a hunting trip in Africa, was wakened one morning with sudden palpitation and extreme prostration, and felt as though he were dying. During the attack, which stopped 24 hours later after he had taken seven grains of quinidine, his heart was completely irregular and the ventricular rate 150. He was 44 and showed no abnormal signs; in the next three years he had only two short sharp attacks.

Again, Case 2 was without symptoms, but had slight mitral stenosis. In her second attack, which lasted 28 hours, she was in a state of collapse and was cold and sweating with a heart-rate of over 200; she appeared moribund, but the next day was almost well. Case 7 also illustrates severe and dangerous symptoms.

These attacks, causing such intense distress, and at the other extreme those which were almost imperceptible to the subject, were relatively few. Generally there was discomfort, more or less severe, without complete disability; for example, one doctor was able to carry on his work slowly though he found it very irksome. The temperament of the sufferer is certainly important in this connexion. The following may be taken as representative: one patient 'first noticed fluttering in the chest; could not stand up, was so unsteady; had shooting

[3] What was almost certainly a paroxysm of auricular fibrillation has been described in the literature of the war, when the author was almost exhausted by the hardships involved in escaping on foot from a prisoners' camp: 'Owing to the mud I began to feel frightfully tired. I staggered, and quite suddenly I collapsed and lay on the ground unable to move. I managed to put my hand over my heart and could feel that it was running most irregularly and misfiring in an extraordinary way. After about a quarter of an hour it got much better, so I had a few mouthfuls of bread and went on again' (*The Escaping Club*, by A. J. Evans John Lane, Lond., 1929, p. 224).

precordial pain like neuralgia; exhausted afterwards', and another 'suddenly felt heart racing and absolutely irregular while walking up a hill; vision became blurred and had to sit down and rest; paroxysm lasted two hours'.

Breathlessness was generally present if the attacks lasted longer than a few hours, though even then some patients were just able to carry on light work. The incidence of the more important leading symptoms was as follows:

Palpitation or fluttering, 115 cases, often very severe, 24.

Exhaustion, inability to stand, 46.

Breathlessness, 32, cyanosis, 3.

Faintness, 22, giddiness, 13, sweating, 5, blurred vision, 3.

Left submammary pain, 18, choking or suffocating feeling, 11, anginal (sternal) pain, 4.

Nausea, 5, vomiting, 3, flatulence, 8, abdominal pain, 4, diarrhoea, 2, polyuria, 3.

Exhaustion and inability to stand or to do anything was, after palpitation, the commonest symptom. Were it not for the resulting inactivity, breathlessness would no doubt be much more frequent.

Faintness, loss of consciousness, and giddiness formed the next most important group. Complete loss of consciousness was not common, but occurred in eight patients, who will be considered in more detail, as syncopal attacks in elderly subjects are a difficult medical problem.

Case 84, aged 55, suddenly lost consciousness; when the doctor arrived he found her heart completely irregular and thought she was dying, but in an hour she had made a good recovery.

Case 151, with exophthalmic goitre, fainted and remained semi-comatose for some hours with a 'heart attack'; she was in the same state when seen just after the onset of established fibrillation. Another case, aged 78, often used to 'swoon towards the end of his attacks', when they had lasted from 8–12 hours. The remaining five had frequent paroxysms, in which they sometimes fainted, but the onset was more like an ordinary faint and not absolutely sudden. One of these continued to have similar faints after fibrillation became established. We have seen one man who suddenly fell unconscious in the road with the onset of permanent fibrillation.

Faintness, then, is fairly common in these paroxysms, but actual fainting is unusual and such a sudden complete loss of consciousness exceptional, though Mackenzie described syncope with fibrillation (75), and Clarke (9) and Weiser (104) have reported full details of a few patients they observed.

Paroxysmal fibrillation has been stated to be a frequent feature of vaso-vagal attacks (89). We do not agree that there is any association.

Pain is relatively uncommon and is rarely severe. The site was more often under the left breast than in the sternum, where anginal pain is generally felt; and indeed only four patients had such pain during paroxysms of fibrillation: a case similar to these has been described by Laslett (57). There were two others in whom angina and paroxysms occurred at different times

without any apparent connexion. Anginal pain was, of course, present where fibrillation followed coronary thrombosis, but these patients have not been included here and are discussed later (see page 80), where more details are given about the occurrence of angina.

For the last group of symptoms—nausea, vomiting, flatulence, and abdominal pain—we have only included patients otherwise free from indigestion, in whom it therefore seemed probable that these symptoms were constantly linked with their attacks. There were others who attributed them to indigestion or to indiscretions of diet, but they were not free in the intervals; this has been discussed under aetiology (see page 73).

The size of the heart during the attacks is of interest in connexion with the symptoms produced. Levine and Golden (65) concluded that it was unchanged in most cases; no doubt this is true of the shorter attacks, but in one case an orthodiagram taken during a paroxysm which had lasted for two weeks showed a heart somewhat larger than any of five others taken during normal rhythm in the course of the next two years. Heitz (44) also found it enlarged in some attacks.

Pulmonary embolism and pulmonary oedema. In a recent paper (87) we concluded that pulmonary embolism was a rare complication of these paroxysms. Further study has confirmed this view, although Case 127 had a cerebral embolism a few hours after a long attack, and one other a pulmonary embolism after a short attack, both making good recoveries.

It has been suggested that acute pulmonary oedema is often due to paroxysmal fibrillation. We have found little to support any relationship, and much evidence that the rhythm is normal with acute pulmonary oedema, as it has been in all the cases we have observed.

The duration of paroxysms. The frequency with which paroxysms recur will be dealt with in the section on prognosis, but their duration is discussed here because of its important bearing on classification. In 160 of these patients there had been no attack lasting more than two days. In twenty with frequent attacks, chosen simply because we had good notes of the duration, it was as follows:

Up to 4 hours, four cases;

Up to 8 or 12 hours, four cases;

From 6 or more to 12 or 18 hours, five cases;

From a few hours to 48 hours, four cases;

About 24 to 48 hours, three cases.

Attacks lasting less than an hour are not so likely to be remembered or recorded, though they often occur interspaced with longer ones.

Attacks lasting more than two days were less usual and only occurred in forty patients. Excluding for the present five men, where fibrillation lasted for months, attacks lasting four days or longer were noted in twenty-four patients only; in sixteen of these the absence of more than one or two attacks showed that they were not of the usual recurrent type. In some, fibrillation became

established after one or two paroxysms, e. g. Case 6; in some it was an unimportant incident in the course of heart failure, e. g. Case 30; but in some there was no other evidence of heart disease, e. g. Case 174.

There were therefore only eight of our two hundred where one of the typical recurrent paroxysms lasted more than four days. We have thought it worth recording those where any paroxysm lasted longer than a week.

In Case 7 the only attack lasted thirty days.

In Case 45, with syphilitic aortic incompetence, the only attack lasted three weeks, and stopped during antisyphilitic treatment.

In Case 80, with raised blood-pressure, one attack lasted nineteen days.

In Case 134 attacks which had probably lasted some weeks were carefully observed for nine and twelve days.

In Case 48, with syphilitic aortic incompetence and heart failure, we observed an attack of eleven days which had little effect on the progress of failure; again it was the only known attack.

In Case 47, with congestive failure, there were during two months' observation thirteen paroxysms lasting from three hours to nine days (38). He died about three months later.

There were six other patients where attacks probably lasted two or three weeks, but they were not under careful observation at the time.

Auricular fibrillation interrupted by normal rhythm. Five other cases were really in a class by themselves. In three, all men aged 55–70, fibrillation was present for three, four, and five months. During treatment with digitalis normal rhythm was restored with great advantage, but paroxysms recurred from time to time in spite of digitalis, and ultimately fibrillation ruled (e. g. Case 97).

Case 149 illustrates another type. He was admitted to hospital with exophthalmic goitre, which had been present for fourteen months (basal metabolism increased 42 per cent.), and with fibrillation, which had probably been present for five months. Two months later three-quarters of his thyroid was removed and normal rhythm returned on the sixth day after operation, i. e. after seven months of fibrillation. Such cases have often been described (19, 20, 55, 58). Lea (60) recorded a short interval of normal rhythm after years of fibrillation; but Case 121, where normal rhythm has returned for more than a year without any apparent cause, was less usual.

Classification of paroxysms. The different types of paroxysms have often been noted. Heitz (44) divided them into frequent short and infrequent long attacks (often with more severe symptoms). Fahrenkamp (27) and Gerhardt (34) distinguished the same two groups, the former resembling paroxysmal tachycardia, and the latter having temporary fibrillation for days or weeks. Krumbhaar (54) introduced the term 'transient' for these, and added the type (which had been noted by Vaquez (102) and Mackenzie (74)), where fibrillation occurred for a short time in paroxysms before it became established. The word 'transient' is not accurate as a description since it might be applied to any paroxysm, but

it serves to designate a group differing from the usual type. Most writers have found that the isolated attacks tend to last longer than those which recur frequently, and this was true in our series.

The following seemed a useful classification :—

Class I. Typical paroxysms occurring (*a*) frequently, e. g. Cases 34, 156, and 190, or (*b*) at long intervals, e. g. Case 24. These are comparable in some ways with paroxysmal tachycardia.

More than half of our patients belonged to this class, the proportion being as high as two-thirds in those with goitre, high blood-pressure, or myocardial disease; but only about one-third in the rheumatic cases. However, the variety found among the remainder has needed more space, both here and in the appendix, so that we must emphasize this common type, drawing attention to the cases just quoted as representative.

Class II. A short series of paroxysms occurring before fibrillation is established, e. g. Cases 6 and 20. In many of Class I also fibrillation will become established ultimately.

There were about one-eighth of our cases in this class, and half of them had rheumatic valvular disease. They are referred to further under the section on prognosis.

Class III. Very few paroxysms (generally only one), often of longer duration. 'Transient' fibrillation of some authors :

(*a*) in the course of heart failure, often without affecting it;

(*b*) after coronary thrombosis;

(*c*) associated with infections, &c., e. g. pneumonia;

(*d*) with no apparent cause.

Classes (*a*) and (*b*) will now be discussed in more detail. Cases 192 and 200 may be taken as representative of (*c*), and Cases 174 and 191 as representative of (*d*); both groups together did not include more than twenty-five cases, and have already been discussed in the section on aetiology.

Paroxysmal fibrillation in the course of heart failure. These sixteen cases formed a rather heterogeneous group, of which the common feature was progressive heart failure; frequently it made little apparent difference whether there was fibrillation or normal rhythm. Cases 28 and 30 may be taken as examples in rheumatic heart failure. The two patients with infective endocarditis and three of the five with syphilis were of this type. Six others were elderly patients with high blood-pressure or myocardial disease.

Coronary thrombosis and angina pectoris in relation to these paroxysms. Paroxysmal fibrillation is not often a striking feature after coronary thrombosis (85), but if the cases are under continuous observation in hospital it can be noted more often, as in nearly a quarter of the cases described by Levine (62); it is generally without much effect on the course of the illness. The two conditions were associated in twelve of these two hundred cases. In ten the attack of pain was followed within a few hours or days by short paroxysms, which were not recurrent (e. g. Cases 46 and 88); these are of no special interest from

the present point of view, except as evidence of the pathology of some attacks. But Cases 56 and 127 are of interest because, after having ordinary paroxysms of fibrillation for five and nine years respectively, they suffered from coronary thrombosis.

There were six other patients with angina and paroxysmal fibrillation. Case 139 frequently had angina, but only one paroxysm, and that quickly followed the onset of pain. This attack of angina differed in no other way from the attacks during the two years before or the three years after; but so far as we know, and she was in hospital under close observation for several weeks, they were never accompanied by fibrillation. One case had paroxysms on several occasions after attacks of angina, but more often had angina without paroxysms; two others developed anginal pain when their paroxysms had lasted for some time, much as certain patients with paroxysmal tachycardia are known to do. In the remaining two, angina and paroxysmal fibrillation occurred at different times, in the one alternating irregularly, in the other (Case 47), when angina had given place to congestive heart failure. He was 68, and had suffered from angina for four years, after which he became free from it, but developed congestive heart failure; during the last six months of his life he had frequent paroxysms of flutter and fibrillation. Though paroxysms of fibrillation may occur after coronary thrombosis, we can conclude that few of the patients with paroxysms have angina, and it is only rarely that the two conditions are associated.

Association with other irregular rhythms. When patients with frequent *extra-systoles* are watched over a long period, it will be noted that only a small proportion develop paroxysmal tachycardia or fibrillation (5). But there is some association, and especially for a period after the paroxysms extra-systoles may be numerous. Frequent extra-systoles were responsible for unpleasant symptoms quite apart from the main attacks in eight of these, e.g. Cases 34 and 190; they were recorded from time to time in many others.

It is not common for *paroxysmal tachycardia* to alternate with or to precede paroxysmal fibrillation, or for it to change into established fibrillation, though we have a few such examples. Case 26 with mitral stenosis had paroxysmal tachycardia for nine years, and then fibrillation occurred twice in paroxysms before it became established. In Case 23, with slight mitral stenosis, a recorded paroxysm in 1922 was auricular tachycardia; another in 1925 was fibrillation, and a year later this became established. Two patients had paroxysms of tachycardia for twenty to thirty years, and for the last few years paroxysms of fibrillation without it becoming established; both had always been troubled with frequent extra-systoles. We have recently seen a patient with as long a history of paroxysmal tachycardia who finally developed fibrillation; this was arrested by quinidine, since when paroxysms of tachycardia have recurred. Two others had attacks which were sometimes fibrillation and sometimes regular tachycardia, the symptoms being very similar; and another had a paroxysm of tachycardia recorded a month before a coronary thrombosis. There are some

few electrocardiograms of fibrillation changing to auricular tachycardia during a paroxysm (40, 69, 84), but this is uncommon.

Parkinson and Bedford (86) concluded that established *flutter* rarely changed to fibrillation, though paroxysms of fibrillation also were noted in seven out of twelve cases with paroxysms of flutter. But paroxysmal fibrillation has a much higher general incidence than flutter, and looked at from this point of view paroxysmal flutter alternating with it is relatively uncommon, being observed in only thirteen of these two hundred cases. They were an atypical group, most of them having signs of gross disease; six are known to have died with congestive heart failure or coronary thrombosis or infective endocarditis, e. g. Cases 88 and 127. Three who are still alive have goitre, and here the combination does not seem of such serious significance.

IV. *Prognosis.*

(*a*) The immediate outlook in the attacks is excellent, and it is more important to inquire how often they are likely to recur and how they will influence the future. It is rare for a patient to be extremely ill during the paroxysm, but then naturally the doctor is anxious to know the danger to life. This is certainly small, yet owing to the association with coronary thrombosis it may happen that the occasion of a paroxysm is also the occasion of death. Thus we saw a man of 55 dying after an attack lasting fourteen hours, with no other apparent cause for failure; but a year before he had been seriously ill, probably with coronary thrombosis.

Case 31 died suddenly and unexpectedly at home; if this was due to a paroxysm she was unique in this series, for she was a young woman with slight mitral stenosis in whom paroxysms of tachycardia and of fibrillation had been observed from time to time during the previous year.

Against these, and much more important from the point of view of prognosis, must be set the rest of the 200 patients, for we are not aware that one of them has died in an attack. Many have been followed for ten years; some have had hundreds of attacks, e. g, Case 190 has survived after more than two hundred lasting longer than an hour in sixteen years.

Another urgent question, if the patient is seen during the paroxysm, is whether it will end spontaneously. It usually lasts less than two days and nearly always less than four, so that earlier than this there is rarely any reason to anticipate permanent fibrillation. After four days it becomes more likely, after seven days probable, after fourteen days almost certain.

(*b*) The ultimate prognosis depends mainly on the heart itself, but also on the frequency with which attacks recur, and on the probability of fibrillation becoming established. These two factors will be discussed independently, though they are themselves influenced by the condition of the heart, e. g. a first attack is not likely to remain the only one if there is other evidence of heart

disease, and fibrillation is more likely to become established if there has been rheumatic carditis.

The frequency of attacks. This is most variable, for at one extreme there are patients with fibrillation present a large part of the time, and at the other those with only a few attacks in several years, e. g. Cases 174 and 191 are in excellent health after an interval of freedom of eight years. But even after such a long period attacks may recur and become more frequent. One man of 57 was free for ten years after his first and for another two years after his second attack, but then began to have them every few months. Another, aged 60, was free for eight years after his first attack, but then they recurred every few weeks for seven years, until fibrillation became established after broncho-pneumonia.

Mouquin (80) has given an interesting example. A man of 30, who had no signs of heart disease, had an attack with sudden onset and offset, with his pulse 'complètement déréglé' five days after his father's death in 1880. There was no recurrence till 1900, and up to the age of 52 (1912) there had been only five attacks; but then they recurred each year, and the electrocardiogram showed they were fibrillation. When 67 they became more frequent, perhaps because he had then cystitis and an enlarged prostate. The recurrence of paroxysms for more than twenty years has been described (23, 43); in one patient fibrillation still recurred, in the other it became established in the twenty-third year.

In general there is a tendency for these paroxysms to become more troublesome with the passage of time; gradually by an increase in their frequency as in those already quoted, or suddenly by the rhythm becoming permanently irregular, as in one case after about three attacks a year for thirteen years, and in another after four or five attacks spread over ten years. Some patients as they get older tolerate them less well, apart from any objective change.

But attacks may continue for long periods without any increase in frequency. One man has had four or five in each of the last ten years, and Case 24 has had eight, fairly evenly distributed throughout the same period. Both were young men without heart disease; but another man, although 61, had only four attacks, each of a day's duration, in the course of eight years. Occasionally the frequency may decrease, even apart from treatment. One patient has carefully recorded his attacks for nine years; some time ago he was having two or three a month, but in the last three years he has only had one each two months.

When there are not more than two or three attacks a year the prognosis is good and the incidence need not increase. More often they are recurrent at shorter intervals, say monthly or weekly, and still the prognosis is satisfactory, in that the incidence need not increase.

When the attacks are very frequent, fibrillation is likely to become established. But Case 168, who for several years has had attacks at least each week, still after eleven years has normal rhythm and is able to work better than some time ago. Even when the attacks are so frequent and irksome

that established fibrillation would seem preferable, it is not always easy to bring about this change with digitalis (see later).

The liability to established fibrillation. During the period of observation—years as a rule—fibrillation has become permanent in one quarter of our patients, and in two or three others during the writing of this paper, so that the final proportion will be higher. There were two almost equal groups: (*a*) in one, paroxysms of the usual type occurred for a long period before fibrillation became permanent; (*b*) in the other, during the months preceding its establishment there were only a few attacks, generally of more than the usual length. In a few patients, mainly rheumatic, fibrillation recurred—probably only for the second or third time—just before death; but could hardly be regarded as established in the usual sense of the term. The figures for the different groups are given in Table IV, and it is clear that aetiology has an important influence.

TABLE IV.

Percentage of Cases where Fibrillation became Established.

Aetiology.	Total number of cases.	Percentage in each group with fibrillation established. (*a*) after a long series of paroxysms.	(*b*) after a few paroxysms only.	Total.
Rheumatic valvular disease	38	18	32	50
Hyperpietic	48	17	10	27
Myocardial	45	18	7	25
Thyroid	28	21	11	32
Other cases, mainly no heart disease	41	5	5	10
All groups	200	15·5	12·5	28

Fibrillation became established in half of those with rheumatic heart disease, but only in one-tenth of those with no heart disease; there was not much difference between the other three groups, which occupied an intermediate position (see Table IV). The average period of time elapsing after the first attack was two years where there was rheumatic heart disease, but over four years in the remainder. There was also a considerable difference between the types (*a*) and (*b*) referred to above.

(*a*) Where there had been a long series of recurrent attacks the aetiology did not make much difference, for in about 15 per cent. of each group fibrillation became established after such a series of attacks, the only exception being the group without other heart disease where the proportion was much less. In all there had been paroxysms for more than a year, the average interval since the first attack being three years in those with rheumatic hearts, five years in those with goitre or high blood-pressure, and eight years in the remainder. In most of them there had been frequent attacks throughout the whole period; in only one had fibrillation lasted two days at a time.

(*b*) Where there had been attacks only during a short period before the permanent onset of fibrillation they were few in number but often lasted

unusually long, as though it had just failed to become established then, e. g. in five of these twenty-five patients paroxysms lasted for four to seven days, and thirteen had only one or two paroxysms. The average time elapsing here between the first attack and established fibrillation was one year; in twelve it was less than six months, and in only five was it more than eighteen months. In this respect Case 20 was the usual, and Case 6 the unusual, type. Half the patients in this group had rheumatic heart disease.

Our conclusions as regards the prognosis and the liability to established fibrillation are summarized at the end.

V. *Treatment.*

The general management of the patient during an attack, the attempt to remove the conditions favouring their recurrence, and the indications for the correct use of quinidine and digitalis will be discussed.

During a paroxysm reassurance will take an important place, especially as the prognosis is so good compared with many other forms of heart attacks. It is desirable that the patient should be at rest, even if not in bed. If the attack is prolonged, the diet must be considered carefully, for flatulent dyspepsia often develops; and a simple hypnotic may be indicated, as we know that attacks often stop during sleep.

After a paroxysm the first object is to decide the nature of the underlying disease. The possibility of hyperthyroidism should never be overlooked, for its correction by thyroidectomy often gives complete relief or great improvement (20, 21, 33, 100). But it is not always successful even when the hyperthyroidism is remedied, as in one case where the attacks were at first controlled by quinidine, but fibrillation quickly became established when it was no longer taken. The special liability to paroxysms just after operation has been mentioned. Their disappearance with the natural cure of exophthalmic goitre is shown in Case 156.

Dietetic and toxic factors must also be considered. The treatment of infections of the urinary tract, especially by prostatectomy, appeared to help in some cases, but not in others. There were four patients in whom treatment with bromide seemed to be effective, but in two of them their work had been substantially reduced at the same time.

There is no convincing chart to show relief with treatment for dyspepsia as, for example, in Cases 34 and 190 with treatment by quinidine or digitalis. But in some few patients, generally those who had not very frequent attacks, dyspepsia seemed an exciting cause, so attention should be paid to this and to the avoidance of large meals. In a case of Edens (24) paroxysms were apparently arrested by vomiting. Similar considerations apply to the abuse of alcohol and tobacco, and reduction or withdrawal of these seemed useful only in a few cases. These factors have been discussed in the section on aetiology.

Quinidine. During the attack the first dose should not be more than 3 grains unless there is previous experience with quinidine in that particular patient; followed if necessary by the same dose or by one of 5 grains after three hours. This dose may be used at first if quinidine is known to produce no toxic effects in that patient; it may be repeated after two hours, but never sooner.

If the attack is of exceptional duration for that individual, it is most important to try and stop it with quinidine; and under these conditions repeated doses, increasing 5 grains each day up to 10 grains t.i.d., are justified.

Many authors have emphasized the value of quinidine in curbing the paroxysms (4, 41, 52, 103, 110). In a recent paper (87) we concluded that quinidine is the best treatment, provided the attacks are of such length or frequency as to justify continuous medication, and that the patient is well enough in the intervals; its use for such a purpose is devoid of risk. We need not therefore discuss this question further, but simply add some patients who have been treated since. Out of thirty-five cases, including these, quinidine abolished or reduced the frequency of attacks in thirteen, and for a time in another five; in six others it helped by cutting short attacks; in ten it was of no use, and in Case 134 it stopped attacks, but increased the degree of cardiac failure.

So in addition to its use in restoring normal rhythm where fibrillation is established, quinidine has won a rightful place in reducing the frequency of paroxysms. Occasionally the improvement is maintained when quinidine is withdrawn. Case 116 had suffered from attacks for fourteen years, until at the age of 58 he was having them each week. He was then treated with quinidine and had only four in the next two years. Since quinidine has been stopped, attacks have been quite occasional.

Sometimes it prevents fibrillation from becoming established. In two cases, at least, this has been exemplified. One man had exophthalmic goitre when 40, and five years later he began to have fibrillation; during three months' observation in hospital it was present for 20 per cent. of the time. With quinidine this was reduced to 5 per cent., but after two years he stopped taking it as the attacks were increasing again. Fibrillation at once became permanent, yet he kept in fair health till his sudden death five years later.

Digitalis producing fibrillation or paroxysms. Mackenzie (73) and Cushny (16) pointed out that digitalis might cause fibrillation, and more recently Resnik (90) produced transient fibrillation in all of seven patients who had congestive failure with normal rhythm, mostly due to syphilitic heart disease. In each case fibrillation followed quickly after full doses of digitalis (0·015 grm. per pound of body-weight) and stopped a few days after it had been withdrawn. Probably these patients were unusually prone to fibrillation because of the myocardial failure. Neuhof (82) has reported the occurrence of fibrillation each time that full doses of digitalis were given to a boy with mitral regurgitation and failure, and recently Schwartz (*American Journal of Diseases*

of Children, March 1930, p. 549) has found it under similar conditions in two children with rheumatic carditis and congestive failure.

Among our cases there were only three where it seemed likely that fibrillation was due to digitalis. A woman, aged 62, had been treated for seven years for high blood-pressure and more recently for increasing oedema of the feet, for which she was given digitalis folia, gr. 3, daily. On the fifteenth day she became much worse with dyspnoea and palpitation, and when seen two weeks later fibrillation was recorded. Digitalis was stopped, and after another two weeks she reported herself better, normal rhythm having returned; it persisted for the next three months, but she died at home five months later. A woman of 31, with mitral stenosis and cardiac failure, was given 30 minims of tincture of digitalis daily for two weeks, when she was found to have fibrillation which persisted a few days after it was stopped. Digitalis given subsequently neither reproduced fibrillation nor relieved her failure; but she died a year later. Case 163 with exophthalmic goitre had his only two known attacks on the second and fifth days after taking 45 minims of tincture of digitalis daily. Four months later fibrillation started again and persisted, this time after taking 30 minims daily for three days.

From these examples and those of Resnik (90) and Gilchrist (35) it appears that digitalis is more prone to produce fibrillation where there is already myocardial failure with normal rhythm. So far as we know it is only under these conditions that it is likely to follow small or moderate doses.

From this point of view it is important to consider the cases where an attempt was made to change paroxysmal to established fibrillation, in view of the frequency of the attacks. In one patient with attacks most weeks during seven years, 1/240 gr. of Nativelle's digitalin taken daily was without effect on the paroxysms for two years, when fibrillation became permanent; and in another the same dose is still without effect. In a third with frequent attacks for two years 1/200 gr. of Nativelle's digitalin each day practically stopped them for three months, until fibrillation became established. In two patients with mitral stenosis and frequent paroxysms 45 minims of tincture of digitalis daily quickly established fibrillation, but in three others, only one with mitral stenosis, similar doses were without effect. These again show that digitalis may serve to produce fibrillation, though not always even when attacks are frequent.

Digitalis in the treatment of paroxysms. This tendency for digitalis to favour the onset of fibrillation has usually been taken as a valid reason for not using it in the treatment of these paroxysms. But they often terminate during such treatment, not only short attacks where digitalization is far from complete, but longer attacks of some days' duration, where it is being given in fairly large doses. Nor does digitalis always convert paroxysmal to established fibrillation with ease: in some patients it actually curbs the paroxysms and in others reduces their frequency.

Three cases have already been quoted where defibrillation was effected by treatment with digitalis—the daily dosage in these three cases and in one seen

since being 30 minims of the tincture in one, and 2 grains of the leaves in the others. Wenckebach has also noted this (105), and Fraser has reported fibrillation giving place to normal rhythm on two occasions with full doses (32).

In other patients attacks stopped while they were taking digitalis, and in four especially it seemed the probable cause. In Case 134 an attack of unknown duration stopped after eleven days on 45 minims of the tincture daily. In three others attacks which had lasted for some days stopped after four, six, and seven days respectively with daily doses of 60 minims. In another three the influence of digitalis was less convincing; but, at the least, the attacks stopped in spite of it, after six, five, and three days of tinct. digitalis, minims 30–45 daily. Hoffman (48) has reported the apparent arrest of attacks with strophanthin.

There were only five cases where the frequency of attacks was greatly reduced by digitalis, so that it could be considered of therapeutic value on this score. This is compared with eighteen where quinidine was found useful in the same way. In Case 190, although the attacks had been getting worse for years, 30 minims of tincture of digitalis each day greatly reduced their length and frequency. In another case 45 minims daily reduced the frequency of attacks for at least a year when quinidine had become ineffective, and similar doses helped in three others.

It will thus be seen that quinidine can be usefully employed to cut short attacks which have lasted more than a few hours, as well as to prevent attacks by its regular administration, but that the effects of digitalis are complicated and even paradoxical.

VI. *Summary and Conclusions.*

In two-thirds of the patients studied the nature of the irregularity was decided by graphic methods.

Aetiology. In 70 per cent. there was structural heart disease, due in about equal proportions to rheumatism, high blood-pressure, or primary myocardial disease. Goitre was causative in 15 per cent., and no underlying cardiac disease was apparent in the remaining 15 per cent. The aetiology is therefore known in 85 per cent. though the provocative stimulus for the attack is obscure.

Symptoms need not be very severe, perhaps no more than palpitation, breathlessness, and inability to continue at work. With a longer attack, or where the heart is already in difficulties, all the signs and symptoms of congestive heart failure may develop. Syncope is rare, and paroxysms are seldom associated with anginal pain, unless both pain and paroxysm result from coronary thrombosis. Between the attacks most patients are able to lead a normal life.

Classification. Paroxysmal auricular fibrillation falls into three main classes, though it is not always possible to assign the first attack to its proper class. (1) Typical recurrent paroxysms (more than half of all these cases).

(2) A few paroxysms preceding the onset of established fibrillation. (3) Single or very occasional paroxysms, often of longer duration; these are seen in the course of congestive heart failure, after coronary thrombosis, with infections such as pneumonia, or with no apparent cause.

Prognosis. (*a*) For the immediate attack the outlook is excellent, as it will seldom persist more than two days. But if it lasts a week permanent fibrillation becomes much more likely, and after two weeks almost certain. (*b*) If a long interval of freedom follows the first few attacks, the prospect for the future is good as they may not recur for years, or not at all, especially when there is nothing else pointing to heart disease. (*c*) If there are only occasional attacks in the course of a year, the liability to any increase in the frequency is small; but unless some effective treatment can be found they will continue as before, and as the years go by some patients will get them more frequently. (*d*) If the attacks recur every few weeks, or more often, they are apt to become more frequent without treatment, and it is probable though never certain that permanent fibrillation will ensue. In some patients, especially in those with rheumatic heart disease, this may happen within a few months after one or two attacks; but if it does not happen so soon it may be postponed for years. Rheumatic heart disease makes permanent fibrillation more likely. The absence of any underlying heart disease makes it much less likely.

Treatment. When a paroxysm of palpitation has been diagnosed as auricular fibrillation, and has lasted more than two or three hours, quinidine will often arrest the attack. Digitalis should not then be given, partly because of its slower action and partly because it may prolong the attack; if, however, quinidine is discarded as ineffective, digitalis should be used, and in large doses if failure supervenes. It will rarely be indicated unless an attack has lasted for days rather than for hours.

Between the attacks, when they recur often enough to require treatment, and when no remediable cause such as hyperthyroidism can be found, quinidine should be used. In the absence of contra-indications as much as 5 grains, three times a day, should be tried before it is stopped. If quinidine fails, and if general measures will not relieve the attacks, most patients would be well advised to bear with them; but should they become unbearable, digitalis must be given, for it may reduce their frequency. Even if it induces permanent fibrillation some patients find themselves better so. Moderate doses, such as 30 minims daily, should first be used and large doses avoided unless permanent fibrillation is desired.

In some patients the presence of a goitre indicates surgical intervention, for the realization that goitre in almost any of its forms may be the cause of these paroxysms is of great importance; our experience leaves us in no doubt about the success of this treatment. Paroxysmal fibrillation may generally be regarded as a troublesome rather than as a serious complication.

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Appendix of Illustrative and Special Cases.

Mitral stenosis. Paroxysm of four days' duration, after pneumonia. Established fibrillation seven years later.

Case 6, aged 34, had mitral stenosis. He had suffered from malaria for eight years in India, and during convalescence from pneumonia he had malarial rigors on three successive days.

He went to work next day not feeling very well, though the temperature had become normal with quinine. Suddenly he had severe palpitation and almost fainted. He drove to the doctor, who said that he was cyanosed and very dyspnoeic, with a pulse that was completely irregular and almost imperceptible. On the following two days he was dangerously ill, and copious blood-stained serum poured from the lungs. On the fourth day his pulse became regular and he improved very quickly. He returned to England, and when examined was quite well except for mitral stenosis and occasional extrasystoles. In 1924 he had a second attack which lasted for two days, but produced less severe symptoms.

In 1929, seven years after the first paroxysm, fibrillation became established (without more than the two paroxysms described); he has made fairly satisfactory progress with digitalis since.

Rheumatic heart disease. Paroxysm lasting thirty days.

Case 7, aged 46, had acute rheumatism as a child, but subsequently worked hard and had seven children without any special difficulty.

In 1914, she was admitted to hospital with fibrillation (EC.), ventricular rate 160. She had aortic and mitral stenosis and signs of failure. She had wakened up eight days before with breathlessness and violent palpitation. Intravenous strophanthin, 1/100 grs., and tincture of digitalis, m. 90, daily for four days, produced no objective or subjective improvement, though they produced striking results in other patients in the ward. After an interval of two days, 60 minims were given daily for six days, but had to be stopped for headaches and vomiting. For five more days she became steadily worse and was thought to be dying. But next day the pulse was regular at 104 (EC. normal rhythm), and she was much better. The paroxysm had lasted thirty days. She went home well three weeks later.

Normal rhythm was present at her visits to hospital during the next five months; she then stopped attending and died one year later.

Rheumatic heart disease. Three paroxysms in two months; then established fibrillation.

Case 20, had chorea at 12 and was in hospital at 21 for her heart, since when she had been more breathless.

Two years later she moved to a tenement with many stairs, and after four days had her first attack of fibrillation, lasting thirty-six hours. Four weeks, and six weeks later, she had two more attacks, each lasting about an hour.

With the fourth attack, less than two months after the first, fibrillation persisted, and she was admitted to hospital. The heart was greatly enlarged, there was aortic stenosis and incompetence, mitral stenosis, and signs of failure. Quinidine was not given because of the size of the heart. She improved with digitalis, but failure returned soon after she left hospital, and she died within three months of the onset of fibrillation.

First paroxysm with dysentery. Subsequent paroxysms, without apparent cause, but only eight in ten years.

Case 24, had chorea as a child, but showed no signs of heart disease, and was accepted for service in Mesopotamia.

In 1918, at the age of 32, he had dysentery; and his pulse then became rapid and irregular (rate 160), but changed to slow and regular again after 48 hours, while he was taking digitalis. The second attack was three years later after influenza.

From 1921–4 he had four more attacks, lasting 24–48 hours. The seventh in 1924 stopped after 5 grains of quinidine, and he took this for some months to avoid a recurrence, as the attacks were getting a little frequent.

From 1924 to 1929 he only had one more attack, for which he again took quinidine.

Short paroxysm in the course of rheumatic carditis.

Case 28 had acute rheumatism when 13, and two years later was in hospital with rheumatic nodules, pericarditis, and mitral stenosis. She remained thin and dyspnoeic, with occasional relapses of pain and pyrexia.

She was readmitted a year later for pyrexia, which lasted for several weeks. After five months in hospital she had auricular fibrillation (EC.) for three hours. In spite of the return of normal rhythm (EC.) failure progressed, and the liver became enlarged for the first time. A week later she vomited and became worse; for the second time the pulse became rapid and irregular and she died ten hours later.

Necropsy showed acute and chronic rheumatic endocarditis of the mitral and aortic valves; enlargement of all chambers of the heart; and chronic pericarditis with adherent pericardium.

Mitral stenosis. Fibrillation changing to normal rhythm after digitalis. Progressive heart failure.

Case 30, was told that her heart was affected after chorea when 5 years old. When 30 she began to suffer from bronchitis, and during her pregnancy, three years later, the cough and dyspnoea became worse, and she sometimes had haemoptysis. The heart was enlarged with a presystolic thrill and murmur.

One month after her confinement there was congestive failure and fibrillation (EC.), though it was not clear how long this had been present. In hospital from the 3rd to the 7th day she was given tinct. digitalis m. 15, four hourly. On the 6th day defibrillation took place (pulse regular 86); but there was no improvement and she died on the 9th day.

Necropsy showed extreme mitral stenosis with dilated auricles (especially the right), thrombosis in the left auricle; and pulmonary and splenic infarction.

Frequent paroxysms during twelve years; arrested by quinidine.

Case 34 had rheumatic fever when 9 and remembered having extrasystoles since childhood.

In 1915, when 37, he had diphtheria and then began to suffer with

paroxysms in which his heart was rapid and so irregular that his doctor had no doubt of fibrillation. The frequency of attacks was very variable; in 1922 he had eleven long attacks (one of eighteen hours) and shorter ones every week; and in 1927 during four months before coming under observation he had twelve attacks, averaging five hours each. There was no enlargement of the heart, no valvular disease, and no increase of blood-pressure; but orthodiagram showed an aortic shadow wide for his age, and the EC. showed a P–R interval of 0·2 second.

Quinidine, grs. iii, b.i.d., was given, and he has been more than two years without attacks of any sort, though they had already been occurring for twelve years. He added that the relief since taking quinidine was much greater than the mere absence of attacks would show; before, almost every occupation gave him extra-systoles, from which he had been almost entirely free since.

Syphilitic coronary occlusion. Paroxysmal fibrillation.

Case 46, had syphilis when 26, but remained well till 42, when he began to have angina on exertion. After eighteen months it became more severe and occurred for the first time, apart from effort, until he was having it daily.

The heart was enlarged to the left and radioscopy showed a dilated aorta. There was an aortic diastolic murmur, and a positive W.R. Among other methods of treatment, digitalis, 60 minims daily for twelve days, did not improve him or affect the heart's rhythm. Two months after this he had sudden palpitation (aur. fibr. EC.), which lasted for a day. He then had no more pain, but died in his sleep on the eighth day.

Necropsy showed coronary occlusion from syphilitic changes, and recent and old myocardial infarction.

Coronary thrombosis. Paroxysmal fibrillation.

Case 88 suffered from giddiness in 1920 when he was 60; his B.P. was 170/100. In 1922 he had severe anginal pain (probably coronary thrombosis), and after it auricular fibrillation, which lasted for two days. He recovered, but in 1924 began to have angina on effort.

Towards the end of 1925 he had sudden severe pain while at stool (coronary thrombosis) and seemed moribund. Later that morning, while the pain still continued and the B.P. was 160/120, a polygraphic tracing showed auricular flutter; he signalled that the pain was over, and thirty seconds later flutter was replaced by fibrillation. Normal rhythm returned the same evening, the B.P. being then 140/90.

He recovered from this attack, but died three months later.

Fibrillation, probably continuous for four months, arrested by digitalis.

Case 97, aged 60, was admitted with slight congestive failure and fibrillation of two months' duration. His B.P. was about 180/110, the W.R. negative, and the heart enlarged; there was fibrillation with wide ventricular complexes due to right bundle branch block. During three weeks in hospital no period of normal rhythm was observed, and he was discharged much better on tab. digitalis folia, grs. 1, o.n.

Two weeks later, the pulse still being irregular, this dose was doubled, and before his next visit normal rhythm (EC.) had returned. Fibrillation had probably lasted more than four months. He continued to have paroxysms, lasting a few hours, about once a week; he stated that he had felt nothing like these before, confirming our view that fibrillation had been constantly present in hospital.

Fifteen months later fibrillation became permanent again with an increase in the congestive failure. Digitalis helped him, but did not again restore normal rhythm.

Spontaneous arrest of long-continued fibrillation.

Case 121, aged 69, was admitted for haematemesis from a gastric ulcer which had reduced his haemoglobin to 34 per cent. He did well after transfusion and operation, but fibrillation was thought to be present throughout his stay in hospital. A year later he became more breathless with gross congestive failure, and on re-admission fibrillation was confirmed (EC.). The heart was enlarged and the arteries thickened (W.R. negative). He improved slowly with digitalis and was discharged after four months, still with some failure; fibrillation was present all the time.

A year later, to our surprise, he had normal rhythm (EC.). There was no failure, and the B.P. was 180/90. The doctor wrote that he had improved steadily, and without digitalis, his pulse having become regular three months after leaving hospital. After another fifteen months his condition was still good, with normal rhythm.

Paroxysms of flutter and fibrillation for nine years; no other signs of heart disease until coronary thrombosis in the ninth year.

Case 127 was active and athletic till 50; he had not suffered from rheumatism or syphilis. In 1918, when 65, he awoke one night with an attack of regular tachycardia. From then onwards attacks recurred each few weeks and lasted some hours or occasionally some days, the pulse being sometimes regular and sometimes irregular; they were often preceded by indigestion. He had smoked heavily before, but now gave it up without arresting the attacks. Between them he was not short of breath and was able to play golf. There were no abnormal physical signs; B.P. 170/90; pulse regular, 48, normal rhythm (EC.) with occasional extra-systoles.

In June 1920 he had an attack of flutter (EC., A. 300, V. 150) which lasted nine days; he remained in bed without digitalis. On the tenth day he walked to the bathroom and fell heavily to the ground, but was not unconscious. Three hours later he was seen with left hemiplegia and impaired speech, the heart rhythm being normal, but eight hours after the onset he had made a complete recovery.

From 1920 to 1926 there was little change; he had attacks most weeks, lasting eight to twelve hours. The pulse was generally regular, probably flutter; but often irregular, and once fibrillation was recorded. Quinidine reduced the frequency of attacks for a time only. In 1926, at 73 years of age, he could still walk twenty miles a day. No method of examination, including electrocardiogram and orthodiagram, revealed any abnormality, and he was thought to have a healthy heart apart from the attacks.

But in 1927 he had coronary thrombosis, and died some months later, ten years after his first paroxysm.

Long paroxysms with congestive failure. Improvement with digitalis. Good health nine years later.

Case 134 was ill for a year with breathlessness, palpitation, and loss of weight, when 31 years old. She improved greatly, but did not become quite normal.

Ten years later she began to get attacks of palpitation and dyspnoea (Dec. 1920), and later oedema of the legs (May 1921). When seen (Dec. 1921) there was fibrillation and gross oedema; the heart was enlarged, but there were no murmurs. Tinct. digitalis, m. 45, daily was given for ten days, when the pulse became regular and polygram showed normal rhythm, fibrillation having lasted more than twelve days. The B.P. was 160/90 and the heart seemed a little smaller than during fibrillation. The oedema quickly disappeared.

During the next three months she generally took digitalis and kept fairly well, only having a few short attacks. But in April she had to go to bed with increasing oedema, and felt ill and unable to do anything till fibrillation stopped after at least nine days, during which she had been taking the same dose of

digitalis. Her paroxysms appeared to be of two types, a few lasting for weeks, and the majority for some hours.

In 1922, as they were increasing, she started on quinidine, grs. 10, daily; and was without an attack for three months, but did not feel better, her weight having gone up from nine to twelve stone, mainly, though not entirely, from oedema. Restriction of diet or of fluids or a salt-free diet did not seem to help. The B.P. was then 140/90 and there was no albuminuria.

Three years later she reported so much improvement that she had been able to start work in 1923. That year there were still many attacks, but in 1924 only one lasting a few hours. She was taking 10 minims of tincture of digitalis daily, which seemed to have been partly responsible for her improvement, but from 1924 onwards this was maintained without any medicine.

In 1929, when 50, she was in excellent health. She was rather overweight and not more breathless than would be expected from this. The aorta was just widened, the heart probably normal in size and certainly no enlargement of the auricles. The B.P. was 150/90 and there were no murmurs. The EC. showed rather low voltage. Her last attack of fibrillation had been more than two years before and had only lasted four hours.

Severe angina pectoris. Paroxysmal fibrillation during one attack.

Case 139 had to give up canteen work on account of breathlessness in 1916, and six years later began to have anginal pain on exertion. This increased in frequency and severity, so that after two years she was almost afraid to walk.

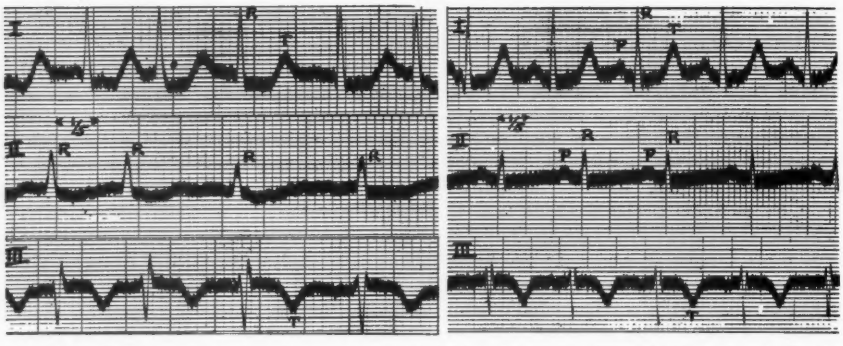

FIG. 4. Electrocardiograms from Case 139; (*a*) during an observed attack of angina with paroxysmal fibrillation; (*b*) 15 minutes later, when the pain had ceased and normal rhythm had returned.

She was then a woman of 60, of calm temperament, but on arrival in the consulting room said an attack was starting. There was severe pain in the upper half of the sternum, passing down both arms to the wrists, and immobility without apparent dyspnoea. Two minutes later, at the height of the pain, the pulse was regular, 104; after another two minutes, the pain persisting, it became completely irregular (EC. fibrillation, Fig. 4 *a*). The pain was relieved, but not abolished, by amyl nitrite. After fifteen minutes it had gone and normal rhythm had returned (Fig. 4 *b*). Radioscopy showed a heart of normal size; there were no murmurs, the B.P. was 135/95, the W.R. negative.

Various methods of treatment did little to relieve her anginal attacks, and though these were witnessed in hospital for weeks fibrillation was not again observed. In 1925 operation was decided on, as she was worn by recurrent attacks. The superior, middle, and inferior ganglia on the left side were removed and a branch of the vagus was divided. At first there was some temporary improvement, but throughout 1926 she was as bad as ever.

In 1928 there was little change on physical examination, B.P. 140/100, and slight cardiac enlargement on radioscopy; but she was definitely better. No doubt between 1922 and 1926 there had been some myocardial changes associated with coronary disease to cause her severe angina; but there was nothing to indicate that the observed attack with paroxysmal fibrillation was coronary thrombosis.

Frequent paroxysms for five years with exophthalmic goitre. Complete cure without operation.

Case 156, aged 38, had suffered from exophthalmic goitre for eight years, and from attacks of palpitation for two years before coming under observation. At first there were paroxysms each week, proved by EC. to be fibrillation. She was unable to take quinidine because of headaches, so was treated with bromides, then with iron, and then with arsenic and bromides at the time she began to improve. The record of her attacks is shown below:

	Number of months.	Average number of attacks each month.	Average duration (hours).
Nov. 1919–Oct. 1921	24	not recorded	not recorded
Nov. 1921–Oct. 1922	12	3·9	8·5
Nov. 1922–April 1923	6	1·3	6·0
May 1923–April 1925	24	0·4	6·5
May 1925–April 1930	60	0	0

Her last attack was in April 1925; in June her thyroid was almost normal, and the pulse had fallen from about 120 to 90; she was practically free from signs or symptoms of hyperthyroidism. In April 1926 her first baby was born, and she has now been in good health for five years without an attack. Her B.P. is now (and has been) normal; the EC. shows nothing but rather flat T waves; an orthodiagram shows no enlargement of the heart.

Exophthalmic goitre. Fibrillation induced by digitalis.

Case 163, aged 56, became tired and breathless with slight congestive failure. He was away from work four months and then only returned with difficulty for another three months. There were few signs of hyperthyroidism, yet his basal metabolism was raised 35 per cent., and he had lost two stone in weight.

Twice while being treated with tincture of digitalis, m. 45 daily, he had short attacks of fibrillation. Four months later he was taken into hospital and at once seemed to get worse. He was treated with tincture of digitalis, m. 30 daily, when fibrillation (EC.) started on the third day, and he became very ill. Omission of digitalis did not stop the fibrillation, nor treatment with it relieve his symptoms. He was thought too ill for quinidine.

On the ninth day of fibrillation he had an embolism of the right femoral artery, and died six days later. Necropsy revealed no source of origin for the embolus; apart from the goitre, the blocked artery, and some enlargement of the heart, he appeared normal.

Goitre. Frequent paroxysms during ten years.

Case 168 began to have paroxysms in 1919 when she was 45, a goitre having been present for ten years; the first lasted six days, but others rarely more than two days. In 1924 a large adenoma and much of the thyroid were removed, but after some temporary improvement in the paroxysms they became more frequent until they were almost daily in 1926. The B.P. was 190/115; there was some enlargement of the heart, but no failure in spite of the frequent attacks. In 1929, ten years after their onset, they still occurred frequently,

though she was rather better and able to do some work. Neither quinidine or digitalis were helpful for long.

Two paroxysms lasting about six days. No recurrence and good health six years later.

Case 174, aged 31, gave no history of previous illnesses and served for four years during the war.

In 1922 he was seen with auricular fibrillation (EC.); he had felt constant fluttering in his chest for five days; but when taken into hospital his pulse became regular the next day. There were no abnormal physical signs, and an orthodiagram showed a heart of normal size and shape; the EC. was normal; the B.P. was 140/90. He was without dyspnoea or any other symptoms except during the attack.

Two years later he had a second attack. He was given 21 minims of tincture of digitalis daily, and normal rhythm returned after five days. He was a little nervous about himself and had given up all alcohol and tobacco (which had always been moderate) since 1922; he had rather increased in weight, probably from taking less exercise.

Six years after the second attack he had not had another; he enjoyed good health and was able to lead a normal life. Physical examination revealed no abnormality.

Paroxysms for seven years. Persistent fibrillation for five years. Normal rhythm restored with quinidine. Good health five years later.

Case 186 had tonsillitis as a child, but never acute rheumatism or any serious illness.

When 24 (1912) he awoke one morning with severe palpitation, breathlessness, and weakness. His doctor found nothing abnormal except the rapid irregular pulse, which he attributed to the strain of hunting, and kept him in bed for a month though the pulse was regular after two days. From 1913–18 he had only five more attacks, each lasting for some hours, and he was able to serve as a combatant officer in France.

He remained well enough to lead a normal life until 1920 when fibrillation started again as he was running upstairs. A week later an EC. showed fibrillation, with a ventricular rate about 100. Fibrillation persisted, but there were no signs of failure, and he was able to get about with few restrictions.

In 1922, after three days' fever (? influenza), he became very ill with heart failure. The ventricular rate was 180; he had Cheyne-Stokes breathing and seemed to be dying. With intravenous strophanthin he gradually improved and left his bed three weeks later. He continued to take digitalis, but was more or less an invalid, having to give up all sport.

In 1925, in the fifth year of persistent fibrillation, he was treated with quinidine by Dr. Cotton and his heart became regular on the sixth day. In 1930, after another five years of normal rhythm, he wrote: 'I was soon able to resume my normal activities, and have continued hunting and playing in tennis, hockey, and polo matches without any trouble whatever.'

His present capacity for exertion and the absence of signs demonstrate that his heart is sound functionally; no doubt his dangerous illness in 1922 was due to a temporary general infection, but his condition at other times from 1920–25 show how much disability may be produced by fibrillation, apart from any other disease of the heart.

Paroxysms increasing in frequency for twelve years. Improvement with digitalis for three years.

Case 190, had no previous illnesses except enteric and pneumonia in 1900 and 1901. In July 1914, when he was 40, he had influenza, and as he was an

officer this was followed by a period of hard work. After three months he began to have palpitation, and extra-systoles were recorded.

Next year he became short of breath on hills and had his first attack of fibrillation when bicycling; this lasted for two hours and left him afterwards with increasing disability, extra-systoles being frequently present and giving rise to great discomfort. Sir James Mackenzie diagnosed paroxysmal fibrillation, but found nothing abnormal on physical examination. The table appended shows the increasing frequency of the attacks during subsequent years till 1926.

In March 1927 he started taking digitalis at the suggestion of Dr. Herapath, whom we wish to thank for later notes. During 1925–26 without treatment he had eighty-four attacks, lasting over an hour, and 140 lasting more than a quarter of an hour. During 1927–28, while taking digitalis, he had thirty-three attacks lasting over an hour and seventy-two lasting more than a quarter of an hour. He wrote: 'Continuous treatment with digitalis has greatly reduced the frequency and duration of the attacks. They are less distressing and the ventricular rate is slower. I can eat, sleep, and get about much better.' The usual dose of digitalis was 30 minims of the tincture daily. At one time it was increased to 40 minims daily, and he then got nausea and diarrhoea and a pulse of 36–42 for two or three days. Even with this full dosage fibrillation did not become established.

Year.	Number of attacks lasting over one hour.	Duration in hours. Average.	Longest.
1915	1	2	2
1916	3	7	12
1917	4	6	11
1918	2	3	4
1919	6	8	14
1920	6	7	9
1921	15	4	7
1922	14	4	7
1923	17	3	7
1924	36	2	8
1925	27	2	5
1926	57	3	10
1927	20	—	5
1928	13	—	4
1929	28	—	7

In 1929 the attacks were getting more frequent in spite of digitalis, but he was anxious to avoid established fibrillation as in the intervals he was fairly comfortable and able to do things. He felt sure that distension after too much food was often the exciting cause, but the history extending over fifteen years without any evidence that he could reduce the attacks by dieting is much against this being an important factor.

Isolated paroxysm. Good health after nine years.

Case 191 had suffered from no illnesses except severe pyrexial diarrhoea in Gallipoli, from which he made a good recovery, so that he was able to continue games vigorously without any symptoms.

In 1920, when aged 30, he played several hard games of tennis as usual. Two days later, after motoring to the station and missing his train, he felt annoyed and suddenly experienced severe palpitation, which still continued the next day. Auricular fibrillation (EC.) was present with a ventricular rate of 90; he had no symptoms except palpitation. He went to bed and normal rhythm returned after forty-eight hours without any other treatment. There were no abnormal physical signs; orthodiagram of the heart showed a normal size and shape; the B.P. was 130/90, and the EC. was normal.

Nine years later he was in excellent health, able to work hard and play

games as before. There had been no more attacks and no change in his physical condition. Just before his attack he had been smoking rather more than usual, 4 oz. instead of 2 oz. a week.

Isolated paroxysm with gastro-enteritis. No recurrence after seven years.

Case 192, a married woman of 48 with six children, gave no history of previous illnesses except that for two years she had occasional attacks of abdominal pain, cured by a day in bed.

In 1923, after tinned salmon for dinner the previous evening, she had violent abdominal pain with vomiting and diarrhoea, and became so cold that she thought she was dying; never before or since has she felt anything like it. She was admitted to hospital the same day, and as the heart was fibrillating she was given tinct. digitalis, m. 45, daily. The diarrhoea and vomiting stopped next day and fibrillation after about sixty hours. Her recovery was uneventful.

Seven years later she had not suffered from another attack and her health was fair, though she was rather tired and depressed. She suffered from vasomotor disturbance so that her fingers readily went dead with the cold. The B.P. was 150/95 and an EC. normal except for rather low voltage. Radioscopy showed that the aorta was wider and more easily seen than usual.

Isolated paroxysm with pneumonia.

Case 200, aged 32, had always enjoyed good health. He had sudden pain in the chest and was admitted to hospital on the third day with lobar pneumonia at the right base. On the sixth day his temperature fell from 104 to 101, but his pulse became rapid and irregular (fibrillation) and he was thought to be dying. He was given 1/200 gr. of strophanthin intravenously four hourly for one day, and afterwards tinct. digitalis, m. 45, daily. On the eighth day his condition was still critical, but on the tenth day his temperature fell to 99, his respiration rate to 20, and on the eleventh day his pulse became regular. He made a good recovery, but it has not been possible to trace him as he was a Swedish sailor.

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CRITICAL REVIEW

THE HARMFUL EFFECTS OF IRRADIATION (X-RAYS AND RADIUM)

By HUMPHRY ROLLESTON

Contents

Introduction 101
The Question of a Stimulating Effect of Irradiation on Normal Tissues . 102
The Question of a Stimulating Effect of Irradiations on Malignant New Growths 104
Injury of the Foetus by Maternal Irradiation 106
Acute Constitutional Symptoms . . 107
Mild 108
Severe 109
Chronic Constitutional Changes . . 115
In the Blood and Blood-forming Organs 115
The Question of Irradiation-induced Leukaemia 117
Aplastic Anaemia 119
Radium Poisoning 119
Local Chronic Lesions 120
Chronic X-ray Dermatitis . . . 120
X-Ray and Radium Malignant Disease 122
Permanent Changes in the Viscera 125
References 126

Introduction.

In November 1895 W. K. von Röntgen (1845–1923) made the momentous discovery of X-rays, which had been mathematically prophesied by Helmholtz in 1893. This announcement in the following month was at once followed by widespread scientific investigation and the application of X-rays in medical diagnosis. In March 1896 it became known that T. A. Edison and W. J. Morton had suffered from conjunctivitis after some hours of exposure to irradiations. Skin lesions, X-ray- or radio-dermatitis, were noticed in the same year.

In April erythema and swelling of the skin (Stevens) and alopecia (Daniel) were reported; later in the year dermatitis in X-ray workers (Leppen; Marcuse) and dermatitis in a patient after irradiation (Drury) were put on record. In February of 1897 Gilchrist collected twenty-three cases of X-ray dermatitis.

In 1897 D. Walsh first directed attention to the acute constitutional symptoms by describing them in X-ray workers, in one of whom the symptoms disappeared after the abdomen was protected by lead. The literature of the accidents and bad effects of irradiation has since become extensive. In 1902 Frieben recorded cancer following chronic ulceration caused by X-rays, in 1911 Hesse collected

[1] Received August 20, 1930.

94 cases (54 in medical men or technicians), and in 1914 Feygin tabulated 104 cases of malignant disease caused by irradiation. In 1911 Krause referred to the death of 54 radiologists from malignant disease caused by irradiation, and in 1922 Ledoux-Lebard estimated that 100 radiologists had died from this cause. Deaths of radiologists, often thus injured before the importance of adequate protection was realized, unfortunately still occur. Dermatitis due to radium, isolated by the Curies in 1898, was reported in October 1900 by Walkoff, and in December of the same year Giesel published an account of the skin lesion caused by exposing his arm for two hours to a celluloid capsule containing radium bromide. In the following year H. Becquerel, the discoverer of radio-activity, and P. Curie described their own experiences; Becquerel carried an insufficiently protected tube of radium salts in his waistcoat pocket for six hours; after a week the skin became red, and eleven days later it ulcerated. Curie repeated Giesel's experiment, keeping radium chloride in contact with his skin for ten hours, and in three weeks' time an ulcer appeared. Dermatitis has since been reported in a number of persons engaged in making radium preparations (Gudzent and Halberstaedter; Ordway; Dautwitz), but not so often in medical men.

With the increase of knowledge, standardization and care in the dosage, and attention to the means of protection now established for patients and radiologists, the undoubted risks of irradiations should be obviated or greatly diminished. It may be noted that this country in 1920 was the first to insist upon the need for protection, and that Dr. Stanley Melville was the moving spirit in this essential reform.

In this brief review of an enormous subject reference will first be made to the question of a stimulating effect of irradiations (X-ray and radium) on normal tissues and on malignant growths, and to the question of the morbid influence of maternal irradiations on the foetus *in utero*. The harmful effects of irradiations will then be further considered under the headings: (1) Constitutional: (*a*) acute (p. 107); (*b*) chronic—changes in the blood and the blood-forming organs (p. 115); (2) Local: chronic lesions, especially dermatitis (p. 120), and malignant growths of the skin (p. 122), and a brief reference to visceral lesions (p. 125).

The Question of a Stimulating Effect of Irradiations on Normal Tissues.

The biological effects of irradiations on living tissues, protozoa and metazoan cells, have given rise to an enormous literature, reviews of which have been given by Pordes, Dorland, Colwell and Russ, Kuhlmann, Warren, and others. The results obtained are obviously dependent on two factors: (i) the character and dose of the irradiations, and (ii) the radio-sensitiveness of the cells. With two variants the problem is complicated, for if one only were effective the matter would be simplified and there would then be either a purely physical or biological question, whereas it is a combined or bio-physical problem.

A much discussed question is whether or not irradiations in small doses can exert a stimulating influence on cells. As this has an important bearing on the harmful effects of irradiation it may be briefly discussed from the point of view (1) of the irradiations and (2) of the cells concerned, though such a distinction may be artificial. (1) According to the Arndt-Schulz law, which has been vigorously criticized in its application to irradiations (Holzknecht, 1923), small doses of an agent stimulate or irritate, whereas medium doses depress, and large ones kill. The results of the numerous investigations undertaken are discordant. Colwell and Russ, summarizing the data obtained in the vegetable kingdom, decide in favour of a stimulating action; but Schwarz, Czepa, and Schindler, using weak doses of X-rays, obtained negative results only, and Nemenow, on the basis of F. Weber's, Iven's, and others' work, argues that the acceleration of flowering obtained is only a quickening of vital processes which thereby are the sooner exhausted. This, however, is not incompatible with the conception of a stimulant. Recently from experimental observations Lallemand concludes that X-rays have not any direct stimulating effect on plants, and that the phenomena which might suggest this are compensatory to damage done. Wigoder and Patten, from investigations on variations in the growth of irradiated bean roots, also found that small doses do not exert any stimulating effect. Numerous observations on protozoa, especially paramecia, and on bacteria have generally been negative; with short X-ray exposures Hance and Clark found that the multiplication rate of paramecia was first depressed and then rapidly became normal; but with longer and repeated exposures the rate of reproduction was slightly stimulated, and it was thought that the action of irradiation might be reversible. Gilman and Baetjer observed temporary stimulation in the development of the ova of *Amblystoma*, and small doses of irradiations were found to accelerate multiplication of the ova of ascarides, and larger doses to inhibit development (Lazarus-Barlow and Bonney). In the metazoa the problem is more difficult. Moppett, working with the chorio-allantoic membrane of eggs, found that rays of adjacent wave-lengths produced very different results—atrophy, stimulation, hyperplasia, and fibrosis. With a small dose of soft X-rays Murphy showed that slight damage of lymphoid tissue was rapidly followed by evidence of stimulation and an increased lymphocyte count in the blood of mice. There appeared to be a definite relation between the amount of damage and the degree of subsequent stimulation; fairly pronounced damage was followed by little, if any, evidence of stimulation, and an exposure not causing damage was not followed by evidence of stimulation. Warren, in a review of the subject, regards Murphy's work as the first real evidence of a true stimulating action exerted by small doses of irradiations. On the other hand, irradiation of tissue cultures *in vitro* with radium (Canti and Donaldson; Canti and Spear) and X-rays (Gaskell; Strangeways and Hopwood; Strangeways and Fell) were negative as regards stimulation. The radio-biological question of a stimulating effect of irradiations is complicated; it has been suggested that the evidence of what has been regarded as stimulation

of cells is really due to the removal of inhibitory influences. Other explanations are that hyperaemia due to the reaction caused by irradiation is responsible for a transient cellular activity (Bianchi), and that the products of more radio-sensitive cells destroyed by irradiation stimulate more resistant cells.

(2) The initial radio-sensitiveness of normal cells varies considerably according to (*a*) their nature (Bergonié and Tribondeau's Law), and (*b*) their state of nutrition and activity. Thus the more radio-sensitive cells are the undifferentiated, such as those of the embryonic and lymphoid tissues, young cells, those in a state of mitosis, or just before the occurrence of mitosis (Strangeways and Hopwood), germ cells, and the epithelium of the small intestine. The influence of the nutritional state of cells on radio-sensitivity is complicated; previous damage, as by irradiation, renders cells, as shown by the skin manifestations, more sensitive, whereas a cachetic condition generally may apparently make the cells of malignant growths irresponsive to irradiations.

As the benefit following X-irradiation in ovarian disorders, such as amenorrhoea and dysmenorrhoea, has been sometimes ascribed to a stimulating action of irradiation, reference to this argument may be made. In mice the sterilization, induced by irradiational destruction of the Graafian follicles of the ovary, has been shown to be followed by all the normal cyclical phenomena except ovulation (Parkes), and in these circumstances oestrin, the hormone causing oestrus, is provided by epithelial cords proliferating from the germinal epithelium after destruction of the Graafian follicles; further, after complete double oophorectomy in mice regeneration of ovarian tissue from non-ovarian tissue, possibly from the mesovarium, may occur (Parkes, Fielding, and Brambell). It therefore appears that any correction of ovarian disorder is not due to a stimulating effect of irradiations on the Graafian follicles, and that any benefit to be ascribed to a fresh supply of oestrin is due to a compensatory regeneration of lutein-like cells and ovarian tissue.

After reviewing the existing evidence on the subject Desjardins arrived at what seems the most probable conclusion, namely, that any apparent stimulation due to irradiation is a temporary phase only and is invariably followed by more or less definite functional or organic deterioration. It would, however, be unwise to consider the subsequent degeneration necessarily permanent, or to lose sight of compensatory effects which may be interpreted as evidence of direct stimulation.

The Question of a Stimulating Effect of Irradiations on Malignant New Growths.

It has often been stated that irradiation of a malignant growth may be followed by increase in its size and by metastases; Schmitt, for example, recorded an 'explosive' dissemination of secondary growths after post-operative X-ray treatment. To quote Sampson Handley (1922), 'small doses of radium stimulate cell activity and mitosis. There is here a distinct danger, for while

the cells near the radium tube may be destroyed, more distant ones may assume increased activity'; and he has since supported this contention by the extension of carcinoma peripherally when radium is inserted into the centre of a growth, and the prevention of its spread when the growth is surrounded by a ring of radium tubes (1929). Biro had the courage to test his opinion on his own person. He had X-ray burns on two fingers; to one he gave a large dose of X-rays, and it eventually healed; the other, after receiving a small dose, rapidly became malignant and was removed. Seitz and Wintz of Erlangen, Thedering, and Zweifel argued that small doses stimulate malignant cells to proliferate, whereas heavy doses do not. Romanis recently brought forward as evidence of stimulation of carcinoma cells by radium the appearance of secondary nodules of growth in the skin at the sites of implantation of radium tubes. Another explanation of the appearance of these growths is that the use of short needles, and too small an amount of radium, provided tracks along which carcinoma cells, not destroyed because insufficiently irradiated, were enabled to grow (Keynes).

The reactions of all malignant tumours to irradiation are said by Dustin to be fundamentally the same and to show three characteristic phases: (1) diminution in the number of mitoses, (2) appearance of atypical mitoses, (3) an amitotic phase which if not accompanied by total degeneration is followed by mitotic activity, at first excessive and then becoming normal. Increase or diminution in the size of a tumour after irradiation is not necessarily due to cellular proliferation or to destruction, for, as Ewing points out, enlargement may be due to vascular congestion, infiltration with leucocytes, serum, or blood, or to bacterial invasion; and on the other hand shrinking of the growth may be due to absorption of fluid. Little or nothing was heard of this stimulating effect of irradiations until intensive X-ray treatment was introduced, whereas the small doses previously used should have led to more frequent metastasis. The stimulating effect of irradiations has been opposed by Hirsch, Borak, Philipp, and Hamperl and Schwarz, on the ground that the histological changes in irradiated carcinoma are always of a degenerative character. Ewing (1922), who also has never seen any definite evidence of stimulation of malignant growths by X-rays, does not accept as properly attested any recorded case. Webster has recently criticized Seitz and Wintz's conception of a stimulating influence of irradiations on malignant cells, and quoted Nather and Schinz's negative results as regards stimulation by irradiating implants of cancer in 200 mice with various doses of X-rays. Roussy and Leroux analysed the incidence of visceral metastases in a rather small number of irradiated and non-irradiated patients with carcinoma and found that they were as frequent, if not more so, in the non-irradiated as in the irradiated.

Increased activity and generalization of a malignant growth, if and when they do occur after irradiation, can be explained, as Holzknecht, Pordes, and Baensch agree, on grounds other than direct stimulation of the malignant cells by the radiations; thus the resistance and inhibitory influence of the surrounding

tissues of the body may be so impaired by the action of the irradiations that any surviving neoplastic cells are enabled to invade the tissue spaces more easily. According to Béclère (1926) impairment of the general resistance and damage to the blood-forming organs, due to excessive radiation, may diminish the inhibitory influence of the tissues and so favour activity of the malignant cells.

At present the stimulating action of irradiations on existing malignant growths cannot be regarded as certainly established.

Injury of the Foetus by Maternal Irradiation.

Damage to the foetus by irradiation of the mother has attracted a good deal of attention both experimentally and clinically. After exposure to X-rays chick embryos have shown retardation or inhibition of development, evidence of degeneration, and after temporary cessation atypical mitosis. Strangeways and Fell's experiments point to the conclusion that these changes are in the main due, not to direct action of the irradiations on the cells, but indirectly to metabolic changes, such as inhibition of gaseous exchange which might result from clotting of blood. H. J. Muller has shown that irradiation of drosophila causes mutations which are transmitted in breeding experiments for many generations according to Mendelian laws, and that the germ plasm is therefore obviously affected. Irradiation of males, it may be noted, caused mutations in the offspring. The mutations were random in distribution, one gene being affected while an adjacent one was unaltered. Schlugt observed impaired development of the descendants of irradiated mice. Bagg, using radium on the parents only of mice, also observed well-marked abnormalities, such as those of the digits, and malformation of the kidneys, the latter appearing in the fifth generation, behaving on Mendelian lines, and persisting in generations for six years. These defects did not occur in control mice. Murphy and de Renyl exposed pregnant albino rats to X-rays, and obtained in a few of the immediate offspring malformations, such as clubbing of the feet and absence of toes, which were not observed in 125,000 control albino rats. Robinson irradiated rabbits, and reported that none of their direct progeny manifested any evidence of degeneration, but his work was criticized as unsound (Little). Garipuy and Estiemny exposed pregnant rabbits to moderate doses of radium without any harmful results. From a summary of the available experimental and clinical evidence of the effects of irradiation on foetal development, Bailey and Bagg in 1923 concluded that experimental irradiation of the gonads before fertilization produces disturbed, abnormal, arrested development in the foetus, resulting in the formation of monsters; irradiation during pregnancy disturbs and arrests development, and causes death of the embryo, stunted growth, cataract, and lesions of the nervous and vascular systems. The clinical data were not extensive, but justified the opinion that irradiation in early pregnancy may lead to foetal death and abortion, subnormal mentality, and other defects; irradiation during later

pregnancy, though it may not produce gross congenital abnormalities, may hinder growth and development after birth.

The serious influence of maternal pelvic irradiation during pregnancy on the foetus is brought out in papers by Murphy and Goldstein, based on a review of the literature and a questionnaire addressed to 1,700 gynaecologists and radiologists in the United States. An analysis was made of 650 cases in which pelvic irradiation by X-rays or radium, before or after conception, had been employed. Pelvic irradiation before conception could not be entirely acquitted of bad effects, but the records of about 260 cases of irradiation (X-rays and radium) before conception showed ten abnormal babies only, and so did not bear out the experimental results. A grave indictment is brought against pelvic irradiation after conception has taken place. Out of seventy-five infants born of mothers irradiated during pregnancy thirty-eight were not healthy, but in ten of these the disability was ascribed to environmental or hereditary factors other than irradiation; of the remainder eighteen were microcephalic idiots. Accordingly it is recommended that curettage should always be performed before pelvic radio-therapy, so as to avoid possible irradiation of a growing embryo. Robinson, who appears to hold a brief for pelvic irradiation, minimizes these conclusions by saying that clinicians, who chanced to see malformed infants born to irradiated mothers, have linked these cases and the experimental data together, and have stigmatized temporary castration, which is an accepted therapeutic procedure by gynaecologists and radiologists all over the civilized world, as a dangerous and unwarrantable form of treatment.

Acute Constitutional Symptoms. Synonyms: Radio-toxaemia, Röntgen-ray Intoxication, Mal de Rayons, Röntgenkater.

Acute constitutional symptoms of a severe character became prominent after the introduction of deep X-ray therapy in which massive doses of deep penetrating rays given by the 'cross-fire' method do not cause skin lesions Thus, to take an extreme example, Rosenthal treated eleven patients with myeloid leukaemia by penetrating irradiations in three directions, with the result that they all were extremely ill and three of them died; the eight survivors, however, were stated to have been much improved for six to ten months. Acute constitutional symptoms after deep radium therapy are less frequent, and when they do occur are shorter and less severe than those produced by X-rays (Regaud; Desjardins). In 1920 Miescher estimated that toxaemia occurred in no less than 40 per cent. of all irradiated patients—a percentage very high unless very minor manifestations are included.

The onset of post-irradiation symptoms, whether mild or severe, may be rapid or be delayed for days; it has been stated that the latent period varies inversely as the intensity and duration of the exposures, a long latent period being usually followed by mild symptoms, whereas the shorter the interval the more severe the constitutional symptoms. But there are many exceptions to

any such rule, and it is quite probable that mild symptoms supervening quite soon after irradiation are due to factors other than those responsible for the grave and alarming constitutional symptoms. Possibly the patient's power of resistance and reactions play a part in determining the time that elapses between the irradiation and the onset of symptoms; but in Rosenthal's eleven cases of myeloid leukaemia the symptoms usually came on at once, whereas in one of the fatal cases the onset was delayed to the third day. It appears probable that in some cases immediate and comparatively mild symptoms ascribed to vitiated air in the X-ray room may be followed, especially after prolonged and intensive X-ray exposures, without any obvious interval by the more severe symptoms due to metabolic disturbance. Few cases showing such an interval have been published, but the late Dr. Robert Knox told the writer of such an occurrence. It may then be difficult to decide on the prognostic significance of symptoms of a comparatively mild character arising immediately after irradiation.

Mild symptoms, namely, malaise, headache, giddiness, faintness, loss of appetite, nausea, salivation, vomiting, and sometimes fever and shivering may begin immediately or an hour after irradiation, pass off in about forty-eight hours, be somewhat alleviated by morphine given during irradiation, and have been compared by Béclère (1921) to sea-sickness. They may be a minor form of the more severe constitutional symptoms, but they have been explained as due to other causes.

An interesting personal account of recurrent subacute symptoms appearing after a latent period of about three weeks, and apparently due to abdominal irradiation, was provided by A. E. Barclay:

> After twelve years' work and much screen examination with inadequate protection during the war, he began to have painless attacks of profuse diarrhoea, at first without other symptoms, but later attended by initial malaise, nausea, vomiting, and on a few occasions by the passage of intestinal casts. Eventually cessation from work became necessary, and the symptoms ceased after three weeks. Return to work was followed by an attack twenty days later, and on eight other occasions an interval of eighteen to twenty days was definitely established. The most efficient means of protection to the abdomen, by a lead apron, was then adopted, with practical freedom from further attacks.

This condition appears to be transitional between the mild attacks and those of the next category (p. 109).

Aetiology: (1) The vitiated air of ill-ventilated X-ray rooms (Wilbert) and the presence of ozone and nitrous acid produced by high-tension currents (Mallet and Coliez) have been incriminated; this factor, though calling for considered prevention, cannot account for all cases, for the symptoms occur after deep radium treatment (H. Pinch), in which the atmosphere is not ionized. (2) High electrical charging of the patient's body, which can be obviated by putting him in communication with the earth (Schrumpf-Pierron); this also does not hold good for symptoms arising in connexion with deep radium therapy. (3) Haemoclasic shock due to destruction of leucocytes (Giraud, Giraud and Parès 1922). (4) Psychological factors to some extent; this view put forward

by Kassabian in 1910 has not received much support, though Dodds and Webster, failing to find any evidence of metabolic disturbance in three cases of very well-marked X-ray sickness, entertained it. Possibly one or a combination of the first three factors may be responsible for some cases. Though Mallet and Coliez drew a sharp distinction between (*a*) the early and comparatively slight disturbance ascribed to a vitiated atmosphere in the X-ray room and (*b*) the later severe manifestation regarded as due to metabolic disorder and cell-destruction, it may be wise to leave open any dogmatic decision on this point; possibly in some instances the early symptoms are due to factors different from those causing the later severe symptoms, whereas in other cases the early disturbance is an attenuated form or early stage of the more severe manifestations.

Treatment of the mild symptoms may be hardly necessary (Bowing; Doub), or they may be guarded against by some of the methods mentioned in the section on the treatment of the severe constitutional symptoms (*vide* p. 114).

Severe constitutional symptoms are nausea, uncontrollable vomiting, sometimes with blood, offensive diarrhoea with the passage of blood, abdominal pain and distension, fever up to 104° F., restlessness, profound prostration, progressive cardiac failure, small rapid pulse, and dyspnoea. When death has occurred it has usually taken place about the fourth day from the onset. In a case fatal on the sixth day Rosenthal recorded flaccid paralysis involving the diaphragm, urinary bladder, and the lower limbs.

The post-mortem appearances of acute constitutional irradiation sickness vary: in Rosenthal's three fatal cases morbid changes were not detected. Destruction and ulceration of the small intestine and colon have been recorded (Franz; Ball; Fischer). These lesions correspond with the numerous experimental results obtained from heavy doses of X-rays over the abdomen (Warren and Whipple and others, *vide* p. 110). The liver cells and bile-duct epithelium have also been found to show evidence of damage (Case and Warthin).

The cause of acute constitutional symptoms has aroused much experimental and clinical investigation, and various explanations have been given. As in the case of the early and mild symptoms, the atmosphere of ill-ventilated X-ray rooms containing ozone and nitrous acid produced by high-tension currents and brush discharges from exposed high-tension wires has been incriminated (Pfahler, 1916; Rieder). Ozone in the proportion of 0·5 mg. per c.cm. of air rapidly causes nausea, headache, irritable cough, and exhaustion, and subsequently chronic blood changes (Konrich). The view that nitrous acid fumes are responsible has been discounted on the ground that they are present in ten times the amount in chemical laboratories without inducing symptoms in the chemical workers comparable to those seen in irradiated patients (Guthmann). A further reason why severe constitutional disturbance cannot be explained, at least exclusively, by atmospheric contaminations in X-ray rooms is that similar symptoms may be induced by radium; these have not only been noticed clinically but the intravenous injection of radium into dogs has been followed by general constitutional symptoms, nausea, vomiting, severe diarrhoea, and

intestinal lesions (Theis and Bagg). As the effects of X-rays and radium on the tissues and metabolism are practically identical, it would appear reasonable to conclude that the post-irradiational (X-ray) symptoms are due to the irradiation and not to concomitant gas-poisoning.

Leaving aside the influence of a vitiated atmosphere which in some circumstances may play an accessory part, the other explanations depend on the destruction of the cellular elements of the body and liberation of products which presumably exert a toxic effect. Every tissue of the body is liable to damage from irradiation, though the degree necessarily depends on the radio-sensitiveness of the tissue, and of course on the character and amount of irradiation. A good example of the difference in reaction shown by different organs to irradiation is that of the larynx, where oedema may occur rapidly and require tracheotomy and the tolerant uterus (Watt). Discussion has ranged over the nature of these products and the way in which they bring about the symptoms.

The agency of protein and other products, from the cellular destruction due to irradiation, in causing acute toxaemia has received much support. Numerous observations point to increased protein metabolism as the result of irradiation, as shown by urinary examination (Bernhardt; Edsall and Pemberton; Hall and Whipple). In the first place the question may be raised whether changes in any one organ are specially prone to cause the general symptoms. In many cases of grave constitutional symptoms the abdomen has been the part intensively irradiated, for example in leukaemia or inoperable malignant disease, and according to Desjardins irradiation of the upper part of the abdomen is specially prone to cause severe symptoms. Irradiation of the pelvic organs for uterine cancer, fibromyomas, and metrorrhagia may be followed by constitutional symptoms usually of a mild character (Béclère, 1921; Chambacher and Decouse; Franz; Knox). Dodds and Webster found that whereas irradiation of the abdomen and spleen was followed by metabolic changes, irradiation of the head, chest, and limbs did not produce these effects. The condition has been regarded as acute uraemia (Andersen and Kohlmann) and due to nephritis (Rosenstein; Warthin, 1907); but Dodds and Webster's investigations did not supply any evidence of nitrogen retention to support this view.

Whipple, in collaboration with Hall and Warren, argues that in dogs a primary acute destructive lesion of the mucous membrane of the small intestine, produced by heavy doses of X-rays from a medium hard Coolidge tube, may be entirely responsible for a non-specific toxaemia, i.e. one not due to any constant bacterial infection. The toxaemia somewhat resembled that described by Whipple in intestinal obstruction and due to a proteose formed in the mucosa of the small intestine, but differed from it in that the coagulation time is shortened (Stephan; Feissly; Paigniez, Ravina and Solomon; Joltrain and Benard; Giraud, Giraud and Parès 1922; Jansen and Schultzer), a result ascribed to thrombokinase liberated from the destroyed leucocytes, whereas in proteose poisoning the coagulation time is prolonged.

Warren and Whipple exposed the thorax of dogs to massive doses of X-rays,

the abdomen being adequately protected. This caused almost complete disappearance of the red marrow from the ribs, but was not followed by constitutional symptoms, thus proving that changes in the bone-marrow and in the intrathoracic lymphatic glands were not responsible for the acute constitutional symptoms; exposures of the abdomen with the thorax protected were constantly followed by severe constitutional symptoms and changes in the mucosa of the small intestine, which were not of the intense inflammatory character that might be expected from bacterial invasion. Mottram and Kingsbury, using a dose of radium sufficient to produce a mild thrombopenia, found that this was followed by inhibition of the secretion of mucus and invasion of the mucosa and blood by bacteria, but that the general or humoral resistance of the rats was not broken down. Intestinal lesions after X-ray exposures have also been observed by Regaud, Nogier and Lacassagne (dogs), Podesta (dogs), Albers-Schönberg, Oberndorfer, Fromme (guinea-pigs and mice), and after radium exposures by Lazarus-Barlow (rats and rabbits). Kolodny produced lesions in the intestine, liver, and spleen of rabbits by X-rays, but Harbinson's experiments were negative as regards intestinal damage though Kupffer's cells in the liver showed signs of injury, and the rabbits died with acute intoxication on the eleventh day.

In 1918 H. E. Schmidt stated that the damage to the intestinal mucosa was the cause of the symptoms in man. It was subsequently suggested that the intestinal lesions were secondary to the toxaemia caused by cellular disintegration (Denis, Martin and Aldrich); this might be regarded as analogous to the 'uraemic' ulceration of the intestines described long ago by Frerichs (1851) and Treitz (1859), and ascribed to the action of blood-borne toxins, to carbonate of ammonia, or to submucous haemorrhages (W. H. Dickinson). The suggestion that the intestinal changes are secondary is contrary to the conclusions of Whipple and his co-workers.

The main source of the protein products liberated by irradiation was considered by Edsall and Pemberton to be the lymphoid tissues which, being highly radio-sensitive and rich in nucleo-proteins, provided toxic substances difficult to metabolize and to excrete. Patients already in a toxic condition were thought to be more prone than healthy persons to manifest constitutional symptoms, as, being already embarrassed in dealing with poisons, the extra strain of a sudden flood of protein products would precipitate grave symptoms. These observers also stated that the toxaemia was not due to renal damage by irradiation, and in an earlier paper in the same year (1897), on the use of X-rays in unresolved pneumonia, suggested that the influence of irradiations on metabolism was mainly to accelerate the action of ferments, a view subsequently taken by Packard. This again raises the question whether or not small doses of irradiations exert a stimulating action, and with regard to ferments also the results are somewhat discordant. According to Henri and Mayer prolonged exposure to radium destroys emulsin and trypsin, whereas Willcock, who confirmed this effect as regards trypsin, pepsin, and ptyalin, showed that tyrosinase was not affected, and suggested that oxydases, being less specialized than digestive

ferments, were not influenced by radium; Neuberg stated that, with the exception of the autolytic enzymes, the intracellular ferments were destroyed; Richards (1917) that short exposures stimulate whereas long exposures inhibit or destroy ferments *in vitro*; and Peterson and Saelhof that moderate doses stimulated mobilization whereas large doses diminished the titre of the serum enzymes. Other reports are to the effect that irradiation does not influence enzymes (Richter and Gerhartz; Colwell). Hussey and Thompson definitely found that the beta rays of radium inactivated pepsin, trypsin, and invertase, and that the amount of trypsin inactivated depended upon the concentration of trypsin and the quantity of radium employed.

That the intestinal lesion is not the sole site of damage responsible for acute irradiation toxaemia is clear, for it may follow irradiation of tumours elsewhere; out of Groedel and Lossen's eighty-one cases symptoms were noticed in every fourth case irradiated over the head and neck, in every third case irradiated over the chest, and in every second abdominal case.

From experimental exposure of the brain to radium, Pendergrass, Hayman, Houser, and Rambo conclude that the radiations kill the nucleus and then the nerve cells which undergo autolysis by the action of intracellular ferments. The lecithin-lipoids were thought to be broken up into choline and neurine, which cause intoxication. As these authors point out, the products of cellular destruction necessarily differ according to the nature of the cells, protein bodies will result from irradiation of smooth muscle in the intestine and uterus, and of lymphoid tissue, and other substances from disintegration of nervous tissue. It has been suggested that the primary action of the irradiations is to upset the colloidal equilibrium of the cell, the injured elements of which are then acted upon by intracellular ferments (Colwell; Wakeley). Observations on the effect of irradiation on the cholesterol-content of the blood are somewhat discordant, but a fall of the blood cholesterol has been recorded (Levy-Dorn and Burgheim), and constitutional symptoms have been thought to be prevented by the administration of cholesterol preparations (Burgheim; L. A. Smith). Burgheim examined seventy-eight irradiated patients and found a constant fall in the cholesterol content.

The different hypotheses as to the mechanism by which disintegration products bring about irradiation sickness will now be mentioned.

Acidosis. Lange suggested, though without any chemical evidence, that acidosis, local or general, is the responsible factor, and recommended treatment by sodium bicarbonate. Some support was given to this view by the production of acidosis in rabbits (Denis, Martin, and Aldrich) and temporarily in man and rabbits just after irradiation (Pannewitz); in their critical paper Dodds and Webster pointed to their observation of a rise in the ammonia coefficient of the urine after irradiation (also found by Theis and Bagg) as in favour of the acidosis view. Negative results were reported by Case and by Golden, and Hussey, working with rabbits, vigorously opposed the acidosis hypothesis, as he found that after irradiation there was a definite uncompensated alkali excess,

and he was able to produce the symptoms of irradiation sickness by intraperitoneal injection of sodium bicarbonate.

Alkalosis, definitely put forward by Hussey's observations, has been supported by Myers and Booher, and by Doub, Bolliger, and Hartman, partly on chemical and partly on clinical or therapeutic grounds, such as aggravation of the symptoms by the administration of alkalis and their alleviation by acids. Doub and his co-workers consider that purines liberated by nuclear disintegration act as strong bases and so produce alkalaemia and more cytolysis; but they assume that usually a compensatory mild acidaemia occurs within twenty-four hours, so that a fatal issue is averted.

The contradiction of these two opposing views suggests that a compromise may be forthcoming in a dual causation of the constitutional symptoms, or in the occurrence of very diverse metabolic changes at different stages of irradiation sickness.

Changes in the distribution of chlorides in the body. As a result of irradiation a fall in the chlorides was found by Nauda in the blood, and by Engelhard and Sielmann in the urine. The latter observers noted a close parallel between the diminished urinary output of chlorides and the degree of the irradiation sickness; and, as there is also a fall in the blood chlorides, believe that the irradiated tissues retain the chlorides. Nauda prevented the occurrence of severe symptoms by giving patients 45 grains of sodium chloride three times on the day before, and 2½ drachms on the day of, irradiation treatment.

Anaphylaxis has, in addition to the rival hypotheses of acidosis and alkalosis, been put forward to explain the mechanism whereby acute constitutional symptoms are precipitated. The protein breakdown as the result of irradiation supplies a basis for the view that irradiation sickness is a form of anaphylaxis. Bergonié, believing that a tissue once irradiated remains for a long time, if not for ever, sensitive to a greater or less degree, regarded this as an indirect or physical anaphylaxis, and to this C. Richet agreed. Now, however, it is unnecessary, in the light of Lewis's work about a liberation of a histamine-like body from the epithelial cells, to invoke a physical rather than a chemical anaphylaxis. Cases in which hypersensitiveness develops after irradiation are not common. Giraud, Giraud and Parès (1921) recorded a case of myeloid leukaemia which tolerated X-ray irradiations for the remarkable period of five years; then after each of the treatments, which were progressively shortened, there followed a short attack, regarded as anaphylactic, of general malaise, intense nausea, copious vomiting, dyspnoea, and vertigo. These symptoms were associated with a fall in the leucocyte count and in the systolic blood-pressure (Widal's haemoclasic crisis), and were ascribed to sensitization due to protein products liberated by destruction of leucocytes by irradiation. The writer has knowledge of a case of chronic lymphoid leukaemia in which, after irradiation had been well tolerated for some time, two severe attacks with characteristic symptoms occurred at five months' interval, the second of which proved fatal. Such an occurrence in leukaemia after irradiation is very rare;

further, the hypothesis that the symptoms are due to destruction of leucocytes would appear to make it probable that these same symptoms would also occur in leukaemic cases which have not been irradiated. Cases of radio-anaphylaxis have been reported by de Courmelles, and Emil Beck mentions patients who after one attack of radio-toxaemia are just as susceptible, if not more so, as they were at first. An obvious objection to anaphylaxis is the occurrence, both experimentally and clinically, of severe constitutional symptoms after the first irradiation. This might be ascribed to inborn hypersensitiveness, but a more commonplace explanation is overdosage or faulty technique. Hall and Whipple from their experimental X-irradiation of dogs definitely opposed the existence of X-ray anaphylaxis, and found some evidence of slightly increased tolerance to a second irradiation, a conclusion endorsed by L. Loeb, who suggested that a fresh growth of cells resistant to irradiations might take place. Although anaphylactic shock is very far from constant in man when it might be anticipated from a previous injection of serum, the rarity of cases compatible with the suggestion that acute constitutional symptoms after irradiation are anaphylactic makes it more reasonable to look for some other explanation.

The complexity of the problem of how the acute constitutional symptoms are produced, though confusing, is not surprising, and, as Flaskamp concludes, it may well be that account must be taken of the combined action of a number of factors—flooding of the circulation with the products of cellular disintegration and their action on the central nervous system and the body as a whole, direct action on the autonomic system, and changes in the endocrine glands.

Treatment. As preventive measures the opposite courses of administering bicarbonate of sodium (Lange) and chlorides (Doub, Bolliger, and Hartman; Cameron and McMillan; Kriser) have been practised by the advocates of the occurrence of acidosis or of alkalosis respectively in irradiation sickness. As mentioned above, Nauda, acting on his observations of the low chloride-content of the blood in irradiated patients, also recommends sodium chloride before exposures. Prophylactic doses of a cholesterol preparation (Burgheim) and of ergosterol (L. A. Smith) have been reported to be very successful. Michalowsky has obtained satisfactory protection by giving ephetonin, a form of ephedrin, by the mouth. On experimental experience Ernst tried and found some benefit from a full vitamin diet. Obvious precautions are proper ventilation of X-ray rooms and care in the dosage and technique of irradiation. In connexion with irradiation of large tumours Beck recommended surgical removal of as much as is possible of the tumour, which should then be irradiated in the open wound. The advantages of this procedure are that the risk of toxaemia is diminished; any discharge from the irradiated tissue escapes into the dressings instead of into the patient's body, and that the dose of irradiations necessary is smaller. The general state of the patient may have a bearing on his tolerance to irradiations (Edsall and Pemberton), and it has been stated that a low systolic blood-pressure and a red blood-count below four millions increase the risk of irradiation (Proust, Mallet, and Coliez). When severe symptoms have set in

transfusion of whole blood and colloidal metals has been recommended (H. Schmidt). Elimination of toxic products may be assisted by free diuresis, and with this object fluids should be freely given by the mouth.

Chronic Constitutional Changes—Effects of Irradiation on the Blood and Blood-forming Organs.

The occurrence of a few cases of leukaemia and of aplastic anaemia in X-ray and radium workers, collected in 1927 by Jaulin, again raises the question whether irradiations in moderate doses can exert a stimulating as well as the recognized degenerative effect in larger doses. There is some experimental work to show that very small doses of long wave-lengths or 'soft' radiations increase the number of circulating lymphocytes, which J. B. Murphy regards as a response by the slightly damaged lymphoid tissues. A transitory increase in the red count occurring immediately after irradiation (Serio and Syrol), after a latent interval of three to five days (Kromeke), or after a short fall in the count (Herzog), has been recorded in experimental animals and ascribed either to stimulation of the bone-marrow by irradiations or to a compensatory reaction of the slightly damaged red bone-marrow. With repeated small doses of irradiations Heineke produced experimentally an increase in the number of red cells. The vast majority of the observations—experimental and clinical—made after repeated exposures point to an inhibitory or destructive effect of irradiations, as shown by a leucopenia.

In 1905 Heineke showed experimentally that large doses of irradiations produced a well-marked fall in the number of haemic lymphocytes due to degeneration in the lymphoid tissues, which Warthin (1906) demonstrated was followed later by changes in the bone-marrow. This has been generally confirmed, for example, quite recently by Piney and Mayneord, and by Wright and Bulman in this country, and corresponds with the view that, like undifferentiated cells and those undergoing or about to undergo mitosis, lymphocytes are highly radio-sensitive, and more so than myeloid tissues.

The blood-count of X-ray workers and those constantly in contact with radio-active substances has often been investigated, especially since the danger of aplastic anaemia was recognized. As might be expected, the blood-picture seen after exposure to irradiations for long periods may differ from that obtained experimentally by one or a few X-ray exposures, and this might be considered to correspond with Warthin's observation that the bone-marrow becomes affected later than the lymphoid tissues. The results reported do not present complete uniformity. Jagié, Schwarz, and Siebenrock in 1911 described a diminution of the granular cells in the blood of X-ray workers; Aubertin in the following year found that there was usually a low white count, but the differential count was variable, and in some instances there was an eosinophilia, whereas Jagié and his collaborators had observed a diminution of the eosinophils. H. Béclère (1912), among eleven radiologists, found a mononuclear

increase at the expense of the polymorphonuclears once only, considerable anaemia twice, and a slight eosinophilia several times. Mottram reported a diminution in both the polymorphonuclears and the lymphocytes. Amundsen found that there was usually a diminution in the total count with a fall in the number of granular cells formed by the bone-marrow and a higher percentage than normal of lymphocytes. Lavedan's recent review of the literature on the condition of the blood in radiologists, including the results of the questionnaire sent by Pfahler (1922) to a thousand radiologists, shows that the consensus of opinion points to a leucopenia with a relative diminution in the polymorphonuclear leucocytes. Barclay and Cox, while admitting that massive doses of high voltage X-rays have a definite effect on the blood, throw doubt on the occurrence of such changes in the ordinary X-ray worker as the result of irradiations, and ascribe blood changes when they do appear to some other factor, most probably vitiated air in ill-ventilated rooms. Repeated examinations of the blood of all the workers in the X-ray department of the Manchester Royal Infirmary, where at the time the conditions of work were far from ideal, failed to show that the staff were working under dangerous conditions.

Among radium workers Gudzent and Halberstaedter found a relative and absolute lymphocytosis averaging 46 per cent., with a diminution of the polymorphonuclears averaging 50 per cent., and a slight fall in the total white count and the haemoglobin, but no change in the reds. Mottram and Clarke reported a diminution in both the polymorphonuclears and lymphocytes; in the workers definitely exposed to radium the red count was low as compared with employees not so exposed, and in some instances the colour-index was raised. This condition was compared with that in three fatal cases (one in a nurse, two in laboratory assistants) of aplastic anaemia at the Radium Institute (Mottram, 1920). Somewhat similar results were published by others (Pfahler, 1922; Williams). Lavedan of the Radium Institute of the University of Paris, where blood examinations have been made every three months since 1921, regards as the characteristic change a mononucleosis, sometimes relative with a leucopenia, sometimes real with a normal or increased leucocyte count. This may be so well marked as to approach an inversion of the normal polymorphonuclear and mononuclear proportions. This change may occur rapidly, but it is not important, as it is not a pre- or sub-leukaemic state and does not favour infections. Its causation is admitted to be obscure. A moderate increase in the number of the red cells was not uncommon and was ascribed to stimulation of the red bone-marrow by irradiations. In some cases there was an eosinophilia, thus agreeing with Aubertin's findings in X-ray workers. Lavedan believes that there is a very decided difference in the susceptibility of individuals to irradiation. Cramer, Drew, and Mottram pointed out that experimentally thrombopenia is caused by the penetrating gamma-rays, which act at much greater advantage than X-rays on the bone-marrow; this was confirmed by Möller. Subsequently, however, repeated small doses of radium were shown to increase the platelet count (Mottram, 1923).

Reference may be made to the question whether the changes in the leucocyte count are due to damage to the circulating cells, to the haemopoietic tissues, or to both. The leucopenia immediately following irradiation has been ascribed to the direct action of irradiation on the leucocytes on the ground that their remains can be seen in blood-films (Minot and Spurling), whereas the prolonged leucopenia has been regarded as due to damage to the haemopoietic tissues (Benjamin, Reuss, Sluka, and Schwarz). Lacassagne and Gricouroff conclude that leucopenia after experimental or therapeutic irradiation is not due to destruction of leucocytes in the blood, either by direct action (Heineke; Russ, Chambers, Scott and Mottram, and Becchini), or by liberation of leucotoxins (Curschmann and Gaupp; Aubertin and Beaujard), but to arrest of leucocyte formation in the damaged leucocyte-forming tissues. On the other hand there is evidence that the phagocytic powers of the polymorphonuclear leucocytes are, as shown by Chambers and Russ (1911) with alpha rays, impaired after irradiation; Knott and Watt irradiated blood outside the body by the hardest available X-rays but could not detect any immediate histological changes; they then employed the biological test of examining the phagocytic power of the polymorphonuclear leucocytes to staphylococci; this showed that the phagocytic power was lost. They also proved experimentally that the damage was done not by the direct action of the rays on the leucocytes but by secondary irradiations in the tissues set up by X-rays. Piney concludes that the early leucopenia is mainly caused by destruction of cells in the circulation and that its persistence depends on damage of the haemopoietic tissue.

It is difficult to estimate the effects on the blood that can be ascribed to irradiation of the reticulo-endothelial system, for there is some uncertainty about the share which the reticulo-endothelial cells take in supplying haemic monocytes. The question whether or not moderate irradiation stimulates the reticulo-endothelial cells has naturally been raised; this is obviously of interest, for increased activity of their undoubted phagocytic power as regards red blood-corpuscles would bear on the production of post-irradiation anaemia. According to G. L. Muller, increased activity of the reticulo-endothelial system produces a fall in the cholesterol-content of the blood, and its decreased activity can be correlated with an increased amount of cholesterol in the blood; this bears on the diminished cholesterol-content of the blood that has been said to occur in irradiated patients (Burgheim) and to have a causal relation to acute constitutional symptoms. There is some experimental evidence in favour of the view that irradiation may stimulate the cells of the reticulo-endothelial system to take up dyes (Pohle, 1929, Benassie); on the other hand the phagocytic power has been stated to be diminished by irradiation (Schürer, Mischtschenko).

The question of irradiation-induced leukaemia. The number of X-ray and radium workers who have become leukaemic is small; out of eight recorded cases, acute or subacute in character, six were in X-ray workers, one in a radium worker, and one in a worker in radium and thorium. This might suggest that, as there are far more workers in X-rays than in radium, the occurrence of

leukaemia is a pure coincidence. This explanation was put forward by Howel Evans and Roberts, who analysed eleven cases reported up to 1928, excluded four, and discussed the mechanisms by which irradiations might bring about leukaemia. On the other hand the greater tendency of radium to cause aplastic anaemia (vide p. 119) might suggest that while its action is more actively destructive, slight doses of X-rays may exert a stimulating action on the bone-marrow (Weil and Lacassagne), or at any rate not prevent it and the lymphatic tissues from undertaking compensatory activity for the destruction of lymphocytes by irradiation. This, though perhaps attractive, is speculative, and at present it is safer to be content with the view that leukaemia, a disease not very uncommon and easily recognized, is when seen in the large number of X-ray workers a coincidence. Aubertin, believing in the stimulating effect of irradiations, exposed guinea-pigs to feeble doses of X-rays for months, but without producing leukaemia. By large doses of X-rays over the spleen K. Ziegler had previously induced a myelocytic reaction in animals, which he explained by the somewhat elaborate hypothesis that damage to the lymphoid tissues in the spleen upsets a mutual inhibitory action between the lymphoid and myeloid systems. It may be added that Gulland was inclined to regard the blood-picture of acute myeloid leukaemia in a case of a woman, frequently irradiated for carcinomatosis, as an erythroblastic and leucoblastic crisis resulting from prolonged irradiation; Davey and Whitby also mentioned this interpretation in reference to their case of acute lymphoid leukaemia in a medical man who had worked much with X-rays. Merklen, Wolf, and Néel reported the occurrence of myeloid leukaemia in a woman four years after prolonged irradiation for a uterine fibromyoma, and, though not dogmatic, were strongly inclined to regard the two events as standing in the relation of cause and effect, thus rather falling into the fallacy of *post hoc, ergo propter hoc*.

The caution necessary in assuming that irradiation may exert a stimulating effect may be illustrated by a case, unpublished on account of insufficient evidence that leukaemia was absent before irradiation, for the notes of which I am indebted to the kindness of Drs. R. C. Jewesbury and D. Leys.

A boy, 3½ years old, with a thymic tumour, enlargement of the tonsils, liver, and spleen, was irradiated with 160 mg. of radium for three hours. A week later the appearance of purpura led to a blood-count being done for the first time; this showed a white count of 625,000, of which 97 per cent. were primitive cells. On the following day glands were palpable in the neck, armpits, and groins, and there was generalized purpura; on the next day the child died in convulsions. Examination after death showed intense lymphocytic infiltration of all the tissues, much hyperplasia of the lymphoid tissue where it is normally present, and massive fibrosis of the thymus.

Cases variously called leuco-sarcomatosis (Kundrat), lymphatic leucosarcoma, or lymphosarcoma, with large tumours in the thymus, retroperitoneal space and elsewhere, and with a normal blood-count at first may, as in Sternberg's leucosarcoma, subsequently show an acute leukaemic blood-picture. When these cases are treated by irradiations in the aleukaemic phase and

leukaemia subsequently supervenes, as in a case recorded by Flashmann and Leopold, who collected five other cases, the question arises whether this is due to a stimulating action of the irradiations or whether it is the natural course of events. In the cases collected by Flashmann and Leopold the tumour formation diminished in size as the result of irradiation, and Evans and Leucutia, who recorded such a case, suggest that by thus prolonging life irradiation allows the leukaemic blood condition to appear more often than would otherwise occur.

Aplastic anaemia. In connexion with the incidence of aplastic anaemia after irradiation it may be pointed out that when this sequence occurs in patients irradiated for leukaemia, as in Ross's case, the issue thereby becomes so complicated that consideration should be focused on, if not confined to, cases, such as those of radiologists and radium workers, in which there has not been any previous disease of the blood-forming organs.

Considering the relatively much larger number of X-ray than of radium workers, the gamma rays of radium appear to have a much greater tendency than X-rays to cause aplastic anaemia; this impression receives support from the experimental evidence that the penetrating gamma rays of radium reach the bone-marrow much more readily than X-rays do (Mottram, 1921). Out of twelve collected cases of aplastic anaemia following long continued exposure to irradiations, and not including those mentioned below under the heading of radium poisoning, seven (Mottram 3, Whitcher 1, Jaulin 1, Brulé and Boulin 1, case of G. Danne) were among radium workers, and one (Weil and Lacassagne) in a thorium worker.

Radium poisoning. Considerable interest attaches to a rare form of industrial risk due to the swallowing of radio-active substances. At Orange, New Jersey, fifteen deaths and five other cases of aplastic anaemia occurred among girls employed in painting luminous dials with a material containing crystallized zinc sulphide and small quantities of radium and mesothorium (Hoffman; Flinn; Martland). Examination of twenty-two other persons employed in this work showed that their blood was not normal; the white count was low, the polymorphonuclears diminished, and the lymphocytes increased (Castle, Drinker, and Drinker). Skin lesions, such as occur in those constantly handling radium, did not attack the victims of radium poisoning. In November 1928 Dr. S. A. von Sochosty, who was technical adviser to the factory and inventor of the luminous paint, died of aplastic anaemia (Martland). The workers pointed the brushes with their lips, tongue, and teeth, thereby ingesting a radio-active substance which when absorbed through the alimentary canal is carried to the skeleton, where most of it has been found, and to the viscera, so that the tissues of the body are constantly exposed to the alpha, beta, and gamma rays. The radio-active substance remains permanently in the body, and was found in one case five years after death, there being 48·3 micrograms of radium in the bones (St. George, Gettler, Alexander, and Muller). In a case examined after death by Martland the ingested radio-active particles collected in the reticulo-endothelial cells, especially of the bone-marrow, where by

continually emitting rays they exhausted the haemopoietic tissues. The bones become brittle, and skiagraphy shows a characteristic rarefaction. Laignel-Lavastine and George observed well-marked fragility of the bones, which appeared spongy, in a patient who for relief of pain had two series of injections of thorium which resembles radium in its action and is often mixed with it. Among the fifteen fatal cases at Orange, New Jersey, two had sarcoma of bone, which Martland and Humphries considered was due, in part at least, to the constant bombardment of the tissues by alpha rays, a condition which never occurs when exposure to irradiations is intermittent and the alpha rays are screened off or absorbed by the superficial layers of the skin. Necrosis of the jaw also occurred in these dial painters (Martland, Coulon, and Knef; Castle, Drinker, and Drinker), and at least seven fatal cases and seven others were known at the end of 1925. This lesion, roughly resembling the 'phossy jaw' of match workers, was regarded as due to gingivitis and consequent infection, caused in the first instance by the radio-active paint being introduced into the mouth, the alpha rays being responsible. Similar necrosis has occurred after therapeutic treatment of oral carcinoma by radium. Although the amount of radium in the paint was small, some of the girls were luminous, and there was evidence that radio-active substance was inhaled and exhaled. That these bad effects, aplastic anaemia and bone changes, were due to sucking the paint brush appears to be clear, as the International Labour Office found from inquiry from watch factories in Switzerland, France, Germany, Austria, Britain, and Belgium, that the painting in those countries is done with a stylet, which is not sucked, and that bad effects have not been observed; in Great Britain the number of workers in 1925 was less than ten, and no serious effects were present then or (Dr. J. C. Bridge tells me) in 1928; but out of seven British women engaged in luminous painting for periods of one to ten years three showed some lymphocytosis and diminution in the number of polymorphonuclear leucocytes (Legge). In the United States radium or mesothorium necrosis was scheduled in 1927 as an industrial disease for which compensation was legalized.

Treatment. Acting on the analogy of the effect of parathormone (Eli Lilly & Co.'s preparation of Collip's parathyroid extract) in lead poisoning, namely, increased excretion of calcium and lead from the bones, Flinn and Seidlin treated these cases with injections of this preparation. The results were very successful, and the radio-activity of the patients was diminished.

Local Chronic Lesions.

Chronic X-ray dermatitis, which has been mainly seen in radiologists and manufacturers of X-ray apparatus, and radium dermatitis, due to alpha and beta soft rays, which is the same change, are serious disabilities, and X-ray dermatitis has often been the precursor of squamous-celled carcinoma. There appears to be a close analogy in this respect with xerodermia pigmentosa, described by Kaposi in 1882. Irradiation dermatitis is an occupational risk

with special characteristics, and in January 1924 was added to the schedule of occupational diseases granted legal compensation under the Workmen's Compensation Act 1906.

The clinical aspects of chronic X-ray dermatitis in radiologists were described by Hall-Edwards (1858–1926), who not only quoted Pitkin's description, but as an unfortunate victim gave a graphic account of the pain in this condition. The change in the hands begins round the base of the nails as an acute erythema which gradually increases. Transverse and longitudinal ridges appear on the nails, which become excessively brittle, tend to separate from the matrix, and eventually thicken and form shapeless masses. The skin becomes uniformly red and atrophied; small warty growths appear, increase in size and number, and when over the knuckles crack on slight exertion and cause much pain. Later the dry thickened skin shows telangiectases, absence of hair, paronychia, and ulcers which are slow to heal and prone to break down. Porter pointed out that, though this keratotic condition resembles the senile form, the combination of juvenile keratosis with ulceration on the dorsum of the hands and fingers seems peculiar to X-ray dermatoses. The freedom of the palms of the hands may be due to the naturally thicker skin there, but the greater liability to exposure on the backs of the hands and fingers is probably the more important factor. The lesions are as a rule slowly progressive. Post-irradiation telangiectases, which have been regarded as compensatory for obliteration of vessels in the corium (Cole), usually appear within two years, and sometimes although an initial erythema was unnoticed; in some instances the interval between irradiation and the appearance of telangiectases is much prolonged, even to fifteen years (MacKee and Eller). Irradiation, like other factors, leads to a condition of vascular inability to respond to histamine and vaso-constrictor substances, this being brought about by liberation in the first instance of a histamine-like body which is six times more concentrated in the epidermal cells than in the dermis (T. Lewis); this inability has been ascribed to injury to the Rouget cells (David). Endothelial proliferation of the vessels and capillary obstruction appear two to four days after irradiation (David; Mottram, 1927). Pohle (1927), using the skin microscope, observed permanent changes, diminished number of capillaries, thickening, dilatation, and inactivity, as did Siedamgrotzky.

Reference may be made to the changes experienced by those handling radium at the Huntington Hospital, Boston, Mass., which were ascribed by Ordway, the physician-in-charge, to the alpha and beta rays. The subjective manifestations were blunting of sensibility in the finger tips, paraesthesia, such as increased sensitiveness to heat or cold, and a varying degree of anaesthesia. The physical changes included flattening of the natural ridges of the skin, with resulting alteration of the finger-prints, thickening of the horny layer of the epidermis with a varying amount of scaling, and failure of the tips of the fingers to regain their shape after pressure—like the pitting of oedema.

Wolbach has given a full account of the progressive histological changes

that lead up to and constitute chronic post-irradiational dermatitis; his description is much the same as those of Lindenborn and of Wyss, who, however, laid special stress on the importance of the vascular changes in causing the dermal lesions. The epidermis is not affected until patches of oedema, passing into necrosis, appear in the superficial collagen fibres of the dermis just under the epidermis. As Rowntree also pointed out, there is much degenerated collagenous material in the dermis. The deeper layers of the dermis become denser and contain much elastic tissue, but few cells, and there is not any attempt at repair of the superficial layers of the dermis. The blood-vessels undergo endothelial proliferation with thickening of the intima and media, and Letulle described fibrinoid necrosis of the vessels; the capillaries are also obstructed, but new formation of both vessels and capillaries occur. After sufficient injury from irradiation complete repair is impossible, and degeneration in the corium and vascular changes continue to progress. The smooth muscle-fibres appear to be enlarged, but this is due to vacuolation and distension with hyaline material. The hair-follicles and the sebaceous and sweat glands completely disappear in cases of long standing. The epidermis is thickened except over foci of acute degeneration of the corium, and Wolbach insisted that the epidermal keratosis and warty formation are secondary to the constant production of small defects in the corium, and are a response to the call for constant active proliferation. The epidermal proliferation is shown by the character of the cells and the presence of numerous mitoses. The proliferating epidermis projects downwards to fill up the gaps formed in the corium, a process explaining the sequence of carcinoma.

Ulceration occurs when the area of degeneration in the corium is too extensive to be bridged over by the epidermis. The floor of the ulcers shows obliterative endarteritis, telangiectases, pigmentary changes, subdermal aneurysms, and haemorrhages from ruptured vessels (Reimer). The ulcers are chronic, tend to penetrate deeply, slough, and, when they heal, to break down again.

Treatment of the ulceration has been of a varied character; surgical removal of the ulcer and of the affected parts, which has been practised to relieve the constant pain, was condemned by Hall-Edwards (1906) as dangerous; carbon dioxide snow (for keratosis), skin-grafting, ultra-violet rays either by the water-cooled mercury vapour apparatus (Sampson) or by the water-cooled arc (Sonne), graduated heliotherapy or irradiation by the quartz light (Desjardins and Smith), and various local applications have been employed. Reimer recommends a lead paste for shallow ulcers and for deep ones after operative measures, whereas Schwarzkopf prefers mild ointments and prolonged baths. Twenty years ago Kassabian, a severe sufferer, collected many methods of treatment.

X-ray and radium malignant disease. Reference may first be made to the experimental production of malignant disease by irradiations, the published records of which are comparatively few and so contrast with the incidence in radiologists. In four out of six mice receiving large doses of X-rays tumours

appeared, three being carcino-sarcoma and one a carcinoma (Jonkhoff). By the prolonged action of X-rays Clunet produced a spindle-celled sarcoma in a white rat, Goebel and Gerard a sarcoma in a guinea-pig, and Bloch a carcinoma with metastases in two rabbits. Daels and Baeten's application of radium in paraffin and talc and also of a watery solution of radium to white rats and white mice was followed by tumour growth in four instances, three of the tumours being spindle-celled sarcoma and one a squamous-celled carcinoma. Clunet's explanation why sarcoma followed irradiation in his rat, whereas squamous-celled carcinoma results in radiologists, was that in rats malignant growths of the skin are predominantly spindle-celled sarcoma, whereas in man the usual form of malignant new growth of the skin is a squamous-celled carcinoma. After irradiation of the spleens of 17–18 day chick embryos cultivated *in vitro* Bisceglie inoculated the tissue into fowls, thus producing a sarcoma which gave rise to metastases in the lungs. In considering the value of this experiment it should be borne in mind that embryonic and sarcomatous tissues are much alike and that injection of very young emulsified embryos into the livers of goats, rabbits, salamanders, and frogs by Birch-Hirschfeld and Garten, though not followed by any permanent tumours, gave rise to nodules of cartilage in the liver and lungs, which grew for a time before being entirely absorbed.

Discussion of the way in which irradiations lead to malignant growth is clearly connected with the question of a stimulating effect of irradiations already mentioned. Wolbach's histological observations are strongly in favour of the view that the primary change is in the underlying connective tissues and blood-vessels and not in the epidermis; this hypothesis for X-ray carcinoma, which agrees with that of Wyss and Lindenborn, fits in with Ribbert's conclusion that changes in the connective tissues precede and are responsible for carcinoma. In this connexion attention may be drawn to Mottram's (1925) suggestion, based on experiments with radium on tissue culture, that malignant neoplasia is due to removal of a normal inhibition of the natural tendency of cells to proliferate. Clinically the usually long interval between the start of chronic X-ray dermatitis and the appearance of carcinoma, during which chronic infection readily supervenes, does not lend any support to a direct stimulation of the cells by irradiations.

Squamous-celled carcinoma is almost always the form of malignant disease which has followed excessive X-ray exposure and long-continued X-ray dermatitis in man. In a few instances sarcoma has been reported.

Porter referred rather hesitatingly in 1909 to two cases of sarcoma, one of which he had previously reported with White. Doubt is naturally justifiable in some cases on account of difficulty in eliminating inflammatory or granulomatous change. A recurrence in Frieben's case of squamous-celled carcinoma was regarded by Unna as a sarcoma. In 1927 a spindle-celled sarcoma arising in the scar of lupus treated by X-rays was published (Camplani), and in 1928 two cases arising in the sites of lupus treated seventeen years previously by X-rays were reported (Alius; Beretvas). But Holzknecht (1929), criticizing Alius' case, contended that from the extreme rarity of such a sequence the incidence of sarcoma is probably not more frequent among patients treated with irradiations

than among other persons. Analogous to the three lupus-sarcoma cases is the sequence of sarcoma developing in the site of a squamous-celled carcinoma of the skin treated by radium (Wagner), and in the site of a similar carcinoma of the tongue treated by X-rays and later by radium (V. Schmidt). Cases of this kind raise several possibilities: that the original tumours were carcino-sarcomas, like the growths produced in mice by X-rays (Jonkhoff), or that the radium, as suggested by Wagner, may have destroyed the carcinomatous elements, or, as Ewing (1918) mentioned in connexion with Hodgkin's sarcoma, that a chronic granulomatous condition may excite sarcomatous change in the surrounding tissues.

Squamous-celled carcinoma has supervened in cases of lupus treated by irradiations, but this is well known to occur in lupus not so treated, Steinhans having collected 83 such cases. In 1905 Da Costa stated that 18 per cent. of the cases of lupus that had been irradiated developed carcinoma, and in 1929 Mrongorius reported that out of 85 patients with carcinoma supervening on lupus 23, or 27 per cent., had been treated by X-rays.

With regard to the source of irradiations followed by squamous-celled carcinoma it is remarkable how very few clinical cases have been reported as due to radium, even when the much commoner and longer-established use of X-rays, which obviously is a factor, is taken into account. Cases have been recorded by McNeal and Willis, and by Thomson and Wakeley. Dr. W. Cramer has kindly given me a reference to a case reported in Laborde's book, *La Curiethérapie du Cancer*, 1925, and Dr. Mottram has seen two unpublished cases; probably it is not so rare as the recorded cases might suggest. Although most often seen in radiologists and manufacturers of X-ray apparatus, X-ray carcinoma occurs in patients who have undergone treatment by irradiations; in 1914 Feygin collected six cases of this kind. One of the earliest victims of X-ray carcinoma was a man engaged in the manufacture of X-ray lamps (Frieben, 1902). The interval between the onset of chronic X-ray dermatitis and the appearance of malignant disease is one of years, from four years upwards; the average of thirty-five cases was seven years (Feygin) In some exceptional instances of therapeutic irradiations an interval of many years has been recorded; Polano reported carcinoma of the abdominal wall opening the urinary bladder fourteen years after X-ray irradiation for a uterine fibromyoma, which originally caused ulceration. In one case there was an interval of eighteen years after epilation by X-rays for ringworm before a basal-celled carcinoma of the scalp appeared (Burrows); but the different form of growth from that (squamous-celled) generally recognized as arising after X-rays is noteworthy and naturally raises the question of the responsibility of irradiation; this doubt also applies to the recorded case of multiple basal-celled carcinomas on the trunk of a radiographer (O'Donovan). This rodent ulcer type of growth, however, frequently supervenes on solar dermatitis in Australia (Molesworth), and Edwards, Creed, and Colwell have recently recorded a rodent ulcer in the scar of an operation for carcinoma of the mamma, performed fifteen years previously, which had since received ninety-four X-ray treatments.

The age incidence, from 35 to 50 (Roussy), is comparatively early, as com-

pared with that of ordinary carcinoma of the skin, which has been found to be between 55 and 58 (Lane-Claypon). The most frequent site of the growth, which is not uncommonly multiple, as in xerodermia pigmentosa, is on the backs of the hands and fingers, and the hand most exposed appears to be the one more severely affected, the left in radiologists, the right in those engaged in the manufacture of apparatus (Feygin). Other exposed parts, the face and eyelids, may also suffer. Among radiologists carcinoma usually starts in an ulcer, less often in keratotic areas. In patients who have previously suffered an acute X-ray burn the skin which had healed may years later become carcinomatous, or ulceration may persist and carcinoma appear, as in the case of radiologists. The predominating symptom is pain, which may be constant and very severe; it has been ascribed to invasion of the terminations of nerves by the growth or to a neuritis.

Treatment of X-ray carcinoma has naturally been surgical; but Bordier, a victim of the disease, deprecated this as removing nature's barriers to dissemination, and condemned radium on the ground that it aggravates the dermatitis, as occurred in the case of his teacher, J. Bergonié of Bordeaux. Bordier strongly recommended diathermo-coagulation under a local anaesthetic, and Nicholas, also treated in this way, confirmed the benefit obtained. Pfahler (1925) recommended the electro-coagulation or desiccation method originally described by W. L. Clark.

That *permanent changes in the viscera* may result from irradiation, whether given in large doses on one or a few occasions, or in small doses spread over a long period, cannot be doubted, from experimental and clinical observation, such as the production of sterilization in both sexes. As long ago as 1905 unsuspected sterility was found in eighteen persons who had for various periods been exposed to X-rays (Brown and Osgood). As acute degenerative changes have been noted from vigorous irradiation in almost all the organs of the body, it would be natural to anticipate chronic fibrosis as a result. Chronic nephritis has thus been produced experimentally (O'Hare, Altnow, Christian, Calhoun, and Sosman; Hartman, Bolliger, and Doub). Six months after X-ray treatment of tuberculous mesenteric glands in a child Domagk found small kidneys with glomerulo-nephritis, but in three other irradiated patients the lesions were confined to the convoluted tubules. In three patients, two with leukaemia, one with lymphadenoma, who had been treated for some time with X-rays, Warthin (1907) found extensive deposits of lime salts filling the tubules and taking the place of the renal epithelium; possibly this may have been due to mobilization of calcium from the irradiated bones, and so to suggest that visceral changes need not depend entirely on local damage to the organ affected. A patient successfully treated for lymphoid leukaemia by X-rays died a year later with ascites and hepatic cirrhosis, which was ascribed to the damage done by the

products of cell destruction (Mosse), but this seems to be an isolated report of hepatic cirrhosis as a result of irradiation. The acute damage done by irradiation to the intestines, reported by Whipple and his co-workers (p. 110), may persist, and intestinal ulcers have followed X-irradiation in patients (Ball), and locally as a result of X-irradiation of the pelvis (Béclère, 1921) or of the application of radium to the cervix uteri (Dürck). Thus the difficult question to decide must arise how far a peptic ulcer in a radiologist is related to his occupation. It has been stated that there is an undue amount of gastric and duodenal disorder among radiologists (Leggett).

Experimentally deep irradiation of the cardiac area has produced hydropericardium, petechial haemorrhages, and infiltration of the right auricle, especially in dogs (Hartman, Bolliger, Doub, and Smith), and microscopically definite myocardial lesions, such as Zenker's degeneration (Warthin and Pohle), atrophy of the muscular fibres, and when less acute interstitial proliferation going on to fibrosis (Davis). Warren and Whipple, however, failed to produce any change in the heart. Abnormalities in the electrocardiogram, especially inversion of the T-wave in leads I and II, and occasionally auricular fibrillation (Hartman and others) have been reported. In patients irradiated for mediastinal and lung tumours similar myocardial changes have been observed (Schweizer; Hartman and others). But Pfahler (1929) in the discussion of Warthin and Pohle's paper stated that in man these myocardial lesions are certainly not constant. Coronary thrombosis does not appear to have been ascribed to irradiation as might be anticipated from the liability of the blood-vessels to be affected by irradiations.

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THE EFFECT OF OILS ON GASTRIC SECRETION AND MOTILITY[1]

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ALTHOUGH the inhibitory effect of oils and fats on the secretory and motor mechanism of the stomach has been demonstrated by Ewald and Boas (4), Lockwood and Chamberlin (6) and others, no adequate explanation of the manner in which it is brought about nor of any purpose which it serves has followed. The results detailed here represent the first part of an attempt to provide the explanation required.

The observations were made both on patients suffering from various forms of gastric disorder and on subjects who, so far as gastric function was concerned, appeared to be normal. Unless otherwise stated, the stimulus to secretion provided was the ordinary gruel meal. The indicators used in the titrations of free and total acidity were dimethylamidoazobenzene and phenolphthalein respectively. Chlorides were estimated by a modification of Patterson's method (10).

I. *A Comparison of the Inhibitory Efficiency of Different Oils and of Related Substances.*

The effect of oil on the gastric secretion in response to a gruel meal is shown by the lower acidity of many or all of the samples withdrawn as compared with corresponding samples of the control meal. The diminished motility of the stomach which also follows the ingestion of oil results in an extension of the time during which gruel samples may be withdrawn from the stomach, or, if the whole stomach contents are withdrawn at any point during the meal, in the greater volume so recovered as compared with the control.

In most of the investigations on this subject olive oil has been largely used as the inhibitory agent, and it is used therapeutically where it is desired to reduce the gastric acidity in cases of ulceration. The investigation was begun by comparing its effect on secretion and motility with that of substances related to it chemically or physically, in order to determine if possible to which of its characteristics its inhibitory properties are due. The oils are glyceryl esters of higher fatty acids, olive oil being the glyceryl ester of oleic acid. The following

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classes of related substances were accordingly tested:—(1) Glyceryl esters of higher fatty acids other than oleic, i.e. oils other than olive oil. (2) Esters of higher fatty acids other than glyceryl esters. (3) Glyceryl esters of lower fatty acids. (4) Glycerol. (5) Higher fatty acids. (6) Alkaline salts of higher fatty acids. (7) Liquid paraffin.

1. *The relative efficiency of different oils.* To enable the oils to be placed in order as regards inhibitory efficiency the results which followed the administration of an ounce of the respective oils twenty minutes before the meal were classified into four groups. In the first group were placed those cases in which a marked effect was obtained, i.e. where hyperacidity was reduced at least to hypoacidity, or where normal acidity or hypoacidity was reduced to a more or less complete achlorhydria for one to two hours. The fourth group comprised the cases in which no definite effect was obtained. The remaining cases showing results intermediate between these two extremes were placed in groups two or three according as a quite definite or only a slight effect was noticed. The classification is of a rather vague nature, but apart from one or two exceptions the cases fell quite clearly into one or another of the four classes. Three points were reckoned for each class 1 result, two points for class 2, and one point for class 3, the sum of the points for each oil being divided by the number of cases in which it was tested, and the results expressed as percentages of the possible totals. The order is shown in Table I.

TABLE I.

Substance tested.	Percentage efficiency.	Cases examined.	Average Iodine value.	Average spec. grav.
1. *Linoleic acid*	*75·0*	*8*	*194·4*	*0·9233*
2. Linseed oil	63·2	57	185.5	0·9363
3. Cod-liver oil	58·3	8	153·8	0·9262
4. Cotton-seed oil	55·6	3	115·0	0·9250
5. Arachis oil	51·7	40	94·2	0·9180
6. Olive oil	42·7	64	83·5	0·9168
7. *Oleic acid*	*41·7*	*8*	*88·2*	*0·8430*
8. Almond oil	36·1	12	96·6	0·9181

The oils having been placed in order, an attempt was made to correlate the efficiency with some physical or chemical characteristic of the respective oils. Speculation had suggested that a relationship might exist to the degree of unsaturation of the constituent fatty acids of the oils, as evidenced by their iodine values, and the oils do to a great extent fall into this order, the less saturated showing the greater efficiency (Table I). Thus linseed and cod-liver oils, which have two double linkages in the molecule, show a clear superiority over olive and almond oils, which have only one. The more marked effect obtained with linseed oil, together with its cheapness as compared with olive oil, suggest its substitution for the latter for the purpose of reducing acidity in gastric and duodenal ulcer, but these advantages are largely counterbalanced by the unpleasant flavour of the grades of linseed oil supplied commercially. This attribute, however, does not account for the superior results obtained, since it is

as effective when introduced into the stomach down the tube as when given by the mouth.

Since the iodine values of the oils run parallel to their specific gravities, the percentage efficiencies show a similar relationship. An association between efficiency and viscosity was also sought, but was less striking. A rough measure of viscosity was obtained by noting the times required for equal volumes of the oils to drip from a burette (Table II).

TABLE II.

Substance examined.	Time in seconds for delivery of 30 c.c. from burette at 18° C.
1. *Linoleic acid*	*238*
2. *Oleic acid*	*365*
3. Linseed oil	420
4. Cod-liver oil	590
5. Olive oil	770
6. Arachis oil	930
7. *Liquid paraffin*	*1960*

Unfortunately, samples of the almond and cotton-seed oils used in the test meals recorded in Table I were not available when Table II was compiled. Further discussion of the results in this sub-section may be conveniently postponed until the results obtained with free fatty acids have been described.

2. *Esters of higher fatty acids other than glyceryl esters.* Ethyl oleate, which differs considerably from the corresponding glyceryl ester in physical characteristics, was selected as a typical member of this class. It was tested in three cases and showed no inhibitory properties; on the contrary, an increased secretion of acid without any definite change in motility was observed (Charts I and II). The ordinate notation on all the charts expresses acidity and chloride concentration as the equivalent number of cubic centimetres of decinormal caustic soda per 100 c.c. of the sample, with one exception to which attention is drawn in the legend of the chart concerned. The volume of residual stomach contents is recorded on the chart in any test which was concluded before the stomach was empty.

3. *Glyceryl esters of lower fatty acids.* These substances were found to be so ill-flavoured as to suggest that even their direct introduction into the stomach down the tube would lead to results from which nothing relevant to the problem at issue would be inferable. This item of the investigation was therefore omitted.

4. *Glycerol.* The administration of half an ounce of glycerol via the tube before the meal was without effect on secretion and motility.

5. *Higher fatty acids.* The quantity given and method of administration were the same as those in the case of the oils. The effect obtained with the free fatty acid of linseed oil, viz. linoleic acid, was even more pronounced than that of the oil itself, but oleic acid was more variable in its action, so that on the whole it was not quite as good as its ester, olive oil. The results are included in Table I, and may be interpreted as supporting the relationship

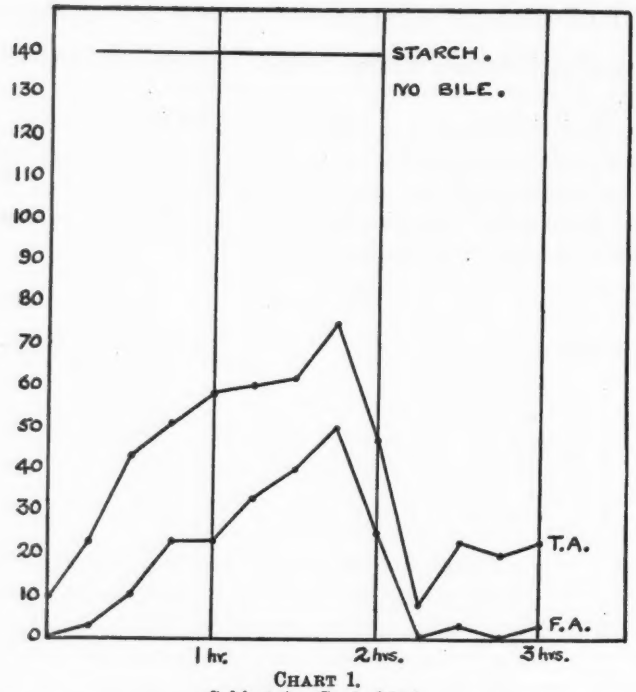

CHART 1.
Subject A. Control test.
In all charts: T.A. = Total acidity. F.A. = Free acidity. T.C. = Total chlorides.

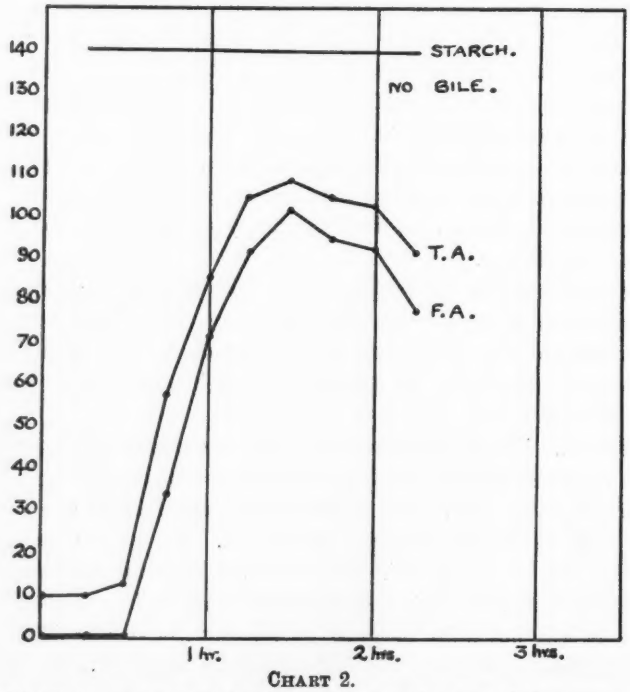

CHART 2.
Subject A. 10 c.c. ethyl oleate through tube 10 minutes before gruel.

already mentioned between the efficiency and the iodine values of the various oils themselves, rather than that between the efficiency and the specific gravity, since the two fatty acids are found in the table adjacent to their esters as regards efficiency and iodine values, whereas the specific gravity relationship is no longer observed in the case of the fatty acids. Similarly, the significance of viscosity as a factor in inhibition is lessened by the results shown in the table of viscosities (Table II), where oleic acid heads the list along with linoleic acid, though its efficiency is much inferior to that of the latter (Table I).

6. *Alkali salts of higher fatty acids.* It has been generally accepted that fat in the process of absorption from the intestine is split into glycerol and free fatty acid, the latter then combining with the alkali of the pancreatic juice to form a soap. It was therefore thought advisable to look for any modifying effect that such salts might show on the gastric response to a gruel meal.

No effect was observed to follow the introduction of sodium oleate solution into the stomach before the meal. If, however, the oleate solution was introduced into the duodenum, gastric secretion was stimulated and higher acidities were found in the test meal. This is in accordance with the results of Babkin and Sawitsch (2), who observed an increased secretion of gastric juice following the introduction of soap into the duodenum in animals.

Roberts (8) reported that although the action of oils resulted in a lower gastric acidity at the end of the first hour, the acidity at the end of the second hour or later was often higher than in the control. This observation was confirmed by Butcher (3), and has been noticed in the present series of tests from time to time. The suggestion was made by Roberts (8) that this might be due to hydrolysis of the oil and the action of the soap so formed in the duodenum. The effect has now been imitated by emulsifying oil with a little oleate and introducing the mixture into the duodenum (compare Charts 11 and 15). At the same time the explanation does not seem to be entirely satisfactory, since the amount of oleate normally present in the duodenum during fat digestion must be very small. Further, it is not clear why the reported effect is not observed more frequently, nor why the inhibitory action of the oil in the above experiment should be seen at once, the oleate effect appearing later.

7. *Liquid paraffin.* One suggested explanation of the effect of oil on the gastric response to food is that it forms a layer over the surface of the gastric mucous membrane, thus protecting it from stimulation by food and substances in aqueous solution within the stomach. If this were the case a mineral oil such as liquid paraffin might operate equally well, but liquid paraffin, given as such, or in an emulsified form as petrol agar (plain), was found to be entirely without action on secretion or motility. Liquid paraffin is miscible in all proportions with the vegetable oils, and the effect of such mixtures appears to be about the same as when the admixed volume of vegetable oil is given alone.

Summarizing the results so far described, it may be said that the different

oils inhibit gastric secretion and motility to varying degrees, a possible connexion existing between inhibitory efficiency and iodine values. Of related substances, only the corresponding fatty acids show inhibitory properties; the remaining substances are either without action, or actually increase secretion.

II. *The Effect of Oil in the Presence of Different Secretory Stimuli.*

The next step was to vary the nature of the secretory stimulus whilst keeping the inhibitory factor constant by giving one ounce of linseed oil

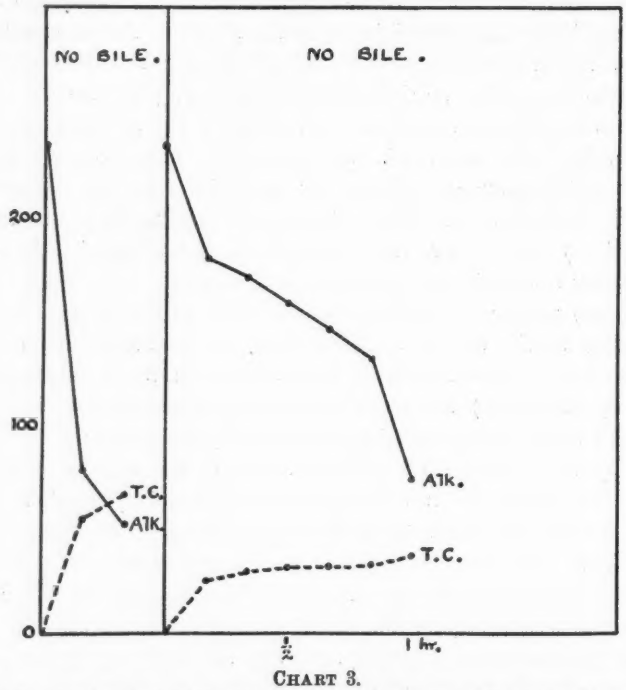

CHART 3.

Subject B. Section 1: Control test, using 500 c.c. sodium bicarbonate solution.
Section 2: As 1, but 1 oz. linseed oil given 20 minutes previously.
Ordinates show alkalinity in terms of c.c. decinormal hydrochloric acid per 100 c.c. of sample.

twenty minutes before the test in each case. It was hoped that a study of any differences in the effect of oil when the secretory stimulus was varied might throw light on the way in which the inhibition is brought about. The different means employed to stimulate secretion, apart from the gruel meal alone, were as follows:—(1) Solutions of sodium bicarbonate. (2) Aqueous solution of caffein, alone and with gruel. (3) Meat extract. (4) Gruel and hydrochloric acid. (5) Gruel and gastric juice. (6) Gruel and histamine.

1. *Solutions of sodium bicarbonate.* When a solution of sodium bicarbonate, concentrated or dilute, was introduced into the stomach the alkalinity

gradually fell as a result of neutralization by the gastric juice secreted whilst the chloride concentration rose by the addition of chloride ion secreted as hydrochloric acid and neutral chloride (Chart 3, Section 1). When oil was given before the alkali the secretion of acid and chloride was diminished, as shown by the more gradual fall in alkalinity and the correspondingly slower rise in chloride concentration (Chart 3, Section 2). This is of interest since bicarbonate is believed to be second only to histamine as a stimulant to gastric secretion. The usual effect of oil on the gastric motility is also evident from the chart.

2. *Caffein solution.* The stimulus to secretion due to caffein was also largely counteracted by oil, whether the caffein was given alone in dilute aqueous solution (gr. v in 500 c.c. water), or added as a concentrated solution down the tube during the course of a gruel meal.

3. *Meat extract.* Meat extract was used as representing the class of substances which stimulate the 'chemical secretion'. The type of chart obtained in the control tests was similar to that which resulted when gruel was used as the test fluid, except that the acidities tended to reach a slightly higher level, whilst the meal left the stomach more readily (Chart 4). Chart 5 shows the effect of oil given before the meat extract; the acidities are lower, and the motility is diminished.

4. *Gruel and hydrochloric acid.* For this test a case which responded markedly to oil was selected, i.e. one in which an achlorhydria of one and a half to two hours resulted. When hydrochloric acid was administered via the tube during such a test in which secretion in response to gruel had been completely inhibited by oil, there was no effect observed other than a rise in the acidity of the gastric contents, which was fully accounted for by the added acidity. This latter point was made evident by dissolving a little creatinine in the hydrochloric acid before it was given; since the creatinine concentration of the samples withdrawn from the stomach ran exactly parallel to their hydrochloric acid content, it follows that no further hydrochloric acid was secreted. The stomach did not empty appreciably more rapidly than in the control test with gruel and oil alone.

5. *Gruel and gastric juice.* A similar negative result followed when gastric juice was given via the tube under similar conditions to the above. Since the inhibitory power of oil is thus maintained when hydrochloric acid or gastric juice is present in the stomach, the administration of oil during a meal in which secretion was proceeding might be expected to lead to its cessation. The reason why this does not always occur in noticeable degree will become clear later.

6. *Gruel and histamine.* A very different result was obtained when histamine was injected subcutaneously during the stage of a gruel meal in which secretion was inhibited by oil. To avoid confusion, only free acidities are shown in the chart concerned (Chart 6). Curve 1 shows the free acidity in the control test with the gruel alone; curve 2 the free acidity when one ounce of linseed oil was given before the meal. The third test was a repetition of the second, but at the point shown by the arrow one milligramme of histamine was

injected. The result was a prompt and copious secretion of acid whilst the emptying time was definitely shortened. Histamine given by the mouth is known to be without effect on gastric function.

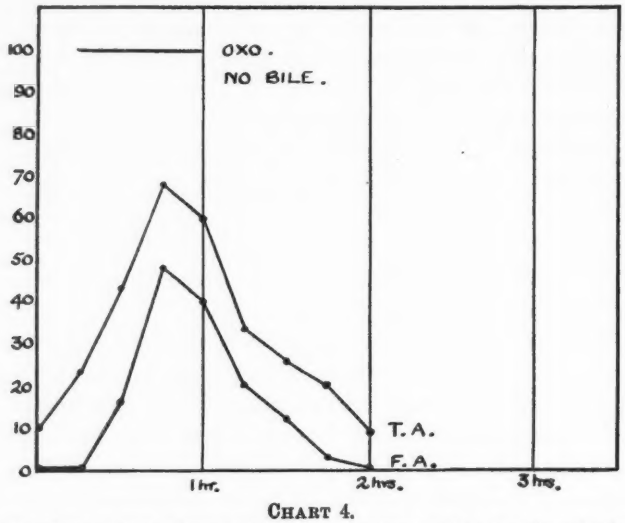

CHART 4.

Subject C. Control test, using 1 pint of meat extract, which in this and other tests had F.A. nil, T.A. 16.

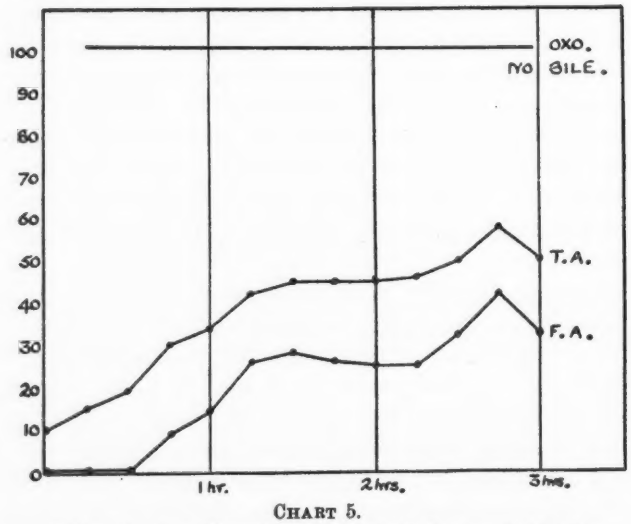

CHART 5.

Subject C. 1 oz. linseed oil 20 minutes before meat extract.

These results indicate, therefore, that oil diminishes the response of the stomach to the presence of food and other stimulatory substances within it, but that it is quite ineffective when the stimulus is supplied by histamine in the blood.

III. *The Effect of Oil on the Component Gastric Secretions.*

As a result of Pavlov's work gastric secretion in response to a meal is believed to comprise two constituent parts, the psychical and the chemical secretions respectively. The question therefore arises whether the inhibitory effect of oil follows from an action on only one of these secretory processes or on both. The evidence about to be brought forward indicates that both processes are affected.

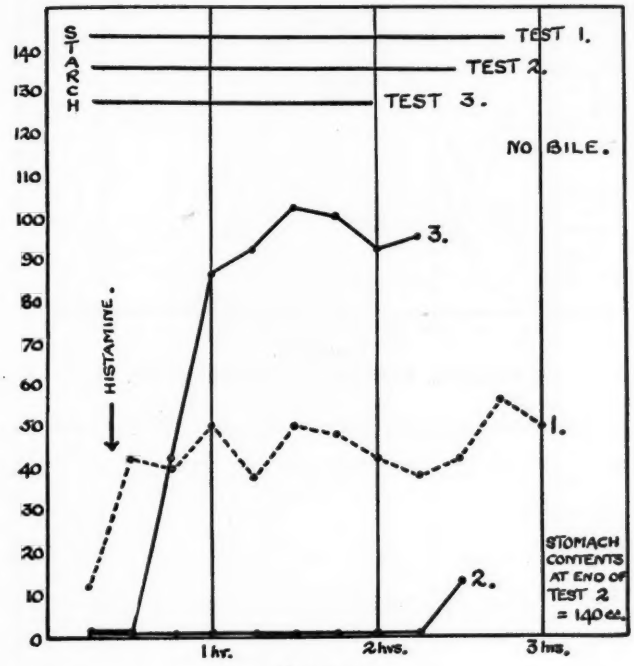

CHART 6.

Subject D. All curves represent free acidity.
Curve 1: Control meal.
Curve 2: 1 oz. linseed oil 20 minutes before meal.
Curve 3: As 2, but with injection of 1 mg. histamine at point indicated by arrow.

A. *The effect of oil on the chemical secretion.* The gruel meal does not excite a chemical secretion until it has undergone partial digestion by the psychical juice, which process results in the production of some unknown secretory substance. The fact that some lowering of acidity follows the administration of oil before a meat extract meal (Charts 4 and 5) does not prove that the chemical secretion is inhibited by oil, since meat extract also stimulates the psychical secretion, which may be the component depressed. This difficulty was overcome by the following series of tests in which meat extract was used as test fluid. A control test was first carried out (Chart 7). In the

next test the psychical secretion was stopped by the injection of gr. $\frac{1}{50}$ of atropine sulphate twenty minutes before the meal was given. The pulse rate rose from 72 to 96, and the patient volunteered the information that his mouth

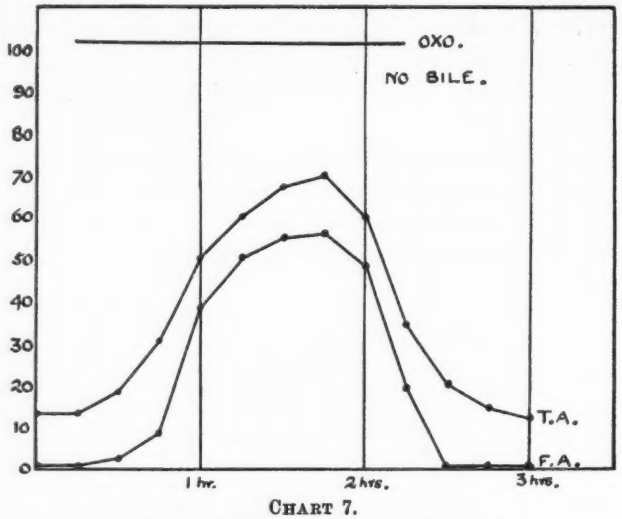

CHART 7.
Subject E. Control test, using meat extract.

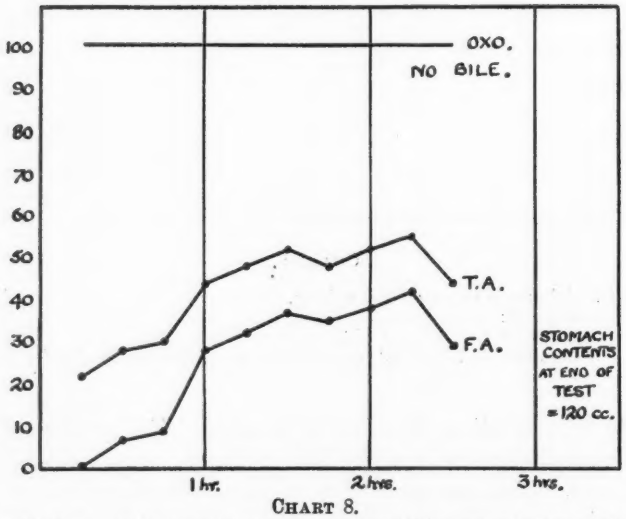

CHART 8.
Subject E. Atropine sulphate gr. $\frac{1}{50}$ injected 20 minutes before meal.

had become very dry. The acidity curves were only slightly lower than the controls (Chart 8). Presumably the chemical secretion was unaffected and accounts for this result. In the third test an ounce of oil was given twenty minutes before the meal. The effect of the oil in this case was shown by the

diminished motility, but no fall in acidity occurred (Chart 9). In the fourth test both atropine and oil were given before the meal. The result was a complete cessation of secretion whilst motility was also inhibited, so that practically

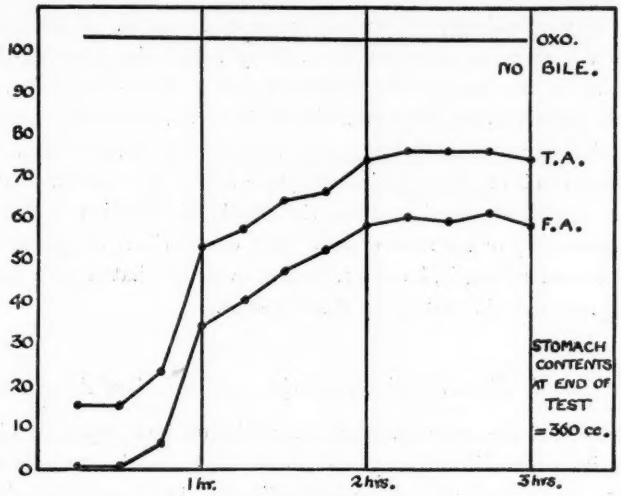

CHART 9.
Subject E. 1 oz. linseed oil through tube 20 minutes before meal.

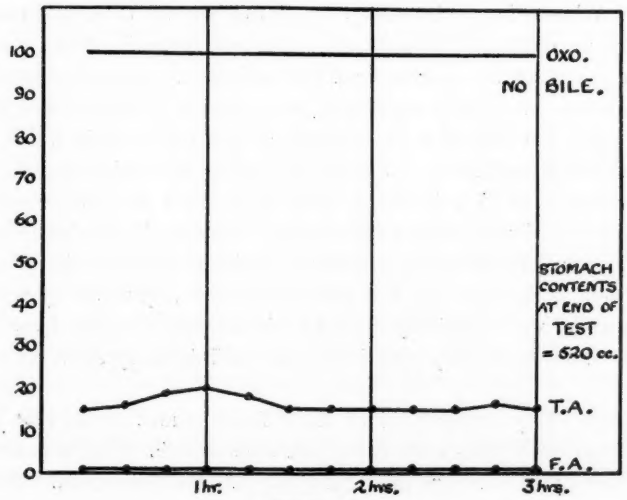

CHART 10.
Subject E. 1 oz. linseed oil through tube and atropine sulphate gr. $\frac{1}{50}$ injected, both 20 minutes before meal.

the whole volume of the meal was recovered from the stomach at the end of three hours (Chart 10). The series of tests was repeated on a second subject with substantially similar results. It seems clear from this that oil inhibits

the chemical secretion, atropine having been shown to inhibit the psychical secretion but not the chemical secretion (Roberts, 1927).

B. *The effect of oil on the psychical secretion.* That oil also exerts an inhibitory influence on the psychical secretion is indicated by the fact that the effect on secretion is observed from the outset of the meal. If the action were confined to the chemical secretion the acidity would rise from the beginning of the test as in the control, any difference due to lack of chemical secretion appearing later in the test. This point is particularly clear in those meals which show an achlorhydria after oil for varying intervals up to two hours.

The effect of oil on the psychical secretion is perhaps more mysterious than that on the chemical secretion, since the psychical secretion is the result of a process essentially of nervous origin. The effect of oil on gastric motility, which is discussed below, is, however, further evidence that it is in fact able to influence a process of this nature by direct means.

IV. *Variations in Effect of Oil due to Different Methods of Administration.*

It was noticed that more pronounced inhibition was frequently obtained if the oil was introduced into the pyloric end of the stomach down the tube than when it was introduced at a point immediately above or below the cardiac sphincter or when it was given by the mouth, provided that not more than a few minutes elapsed between the administration of the oil and the taking of the gruel. When a longer interval was allowed the oil of course reached the pylorus, and no difference between the cases was noticed. When the oil was given after the gruel the results were less satisfactory, though some effect was usually observed. A further significant fact which was noticed was that only traces of oil were recovered in the samples during the meals in which the most marked inhibition occurred, and when the whole remaining gastric contents was withdrawn after $2\frac{1}{2}$–3 hours in these cases, little oil was present, though the volume of gruel was often considerable. Conversely, in those tests where appreciable quantities of oil were present in the samples the inhibitory effect was much less noticeable, and this was not due to loss of oil by withdrawal, since the oil did not invariably appear until the later samples, by which time it was clear from the acidity titrations that the inhibitory effect was not very marked.

The most likely explanation of these facts seemed to be that the main action of the oil took place after it had left the stomach. This was accordingly put to the test by introducing the oil directly into the duodenum. The fasting contents having been withdrawn from the stomach, the tube was passed on into the duodenum and the oil introduced down the tube. The tube was then drawn back into the stomach, and, after withdrawal of any fasting secretion that had collected, the meal was given and proceeded with in the usual way. The inhibitory effect which was obtained was equal to the best results produced when the oil was introduced into the stomach. Although it is possible to infer

when the tube is in the duodenum from the nature of the material withdrawn by the tube, X-ray examinations were made in several of the cases in order to locate the exact position of the bulb of the tube. The results obtained were essentially the same whether the oil was introduced whilst the bulb was in the first part of the duodenum as when it lay in the fourth part. These points are illustrated in Charts 11 to 14.

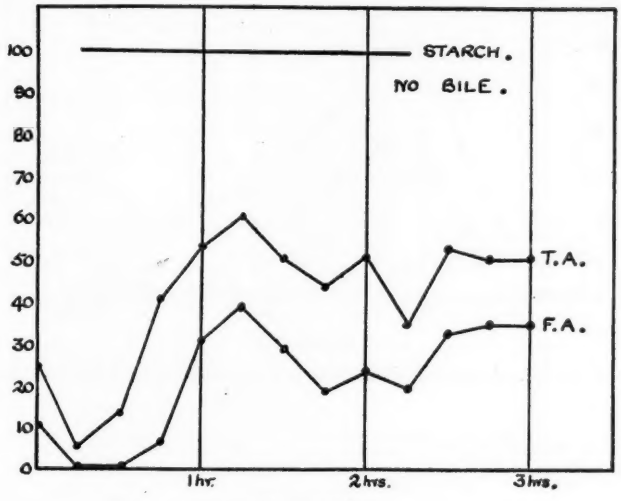

CHART 11.
Subject F. Control test.

Although the evidence is not conclusive it is at least suggestive of the fact that the oil exerts no inhibitory action whilst it remains in the stomach, since, as already stated, poor results were obtained when much of the oil was found in the stomach, and in one case of very severe pyloric stenosis in which, as far as could be estimated, all the gruel and oil were recovered at the end of the meal, no inhibitory effect was observed.

The explanation of the fact mentioned earlier, that oil given during the meal is less effective than oil given before the meal is doubtless that in the former case some time must elapse before it becomes mixed with the gastric contents and passed on to the duodenum in sufficient quantity to produce a noticeable result. It should be noted that if the oil is introduced directly into the duodenum, the gruel may be given *immediately* without any impairment of the inhibitory effect.

V. *The Effect of Oil in Cases of Achlorhydria.*

In cases of achlorhydria the test meal frequently leaves the stomach with greatly increased rapidity. The effect of oil is to delay this process. Thus oil-gruel meals in several cases of pernicious anaemia in which the control meals

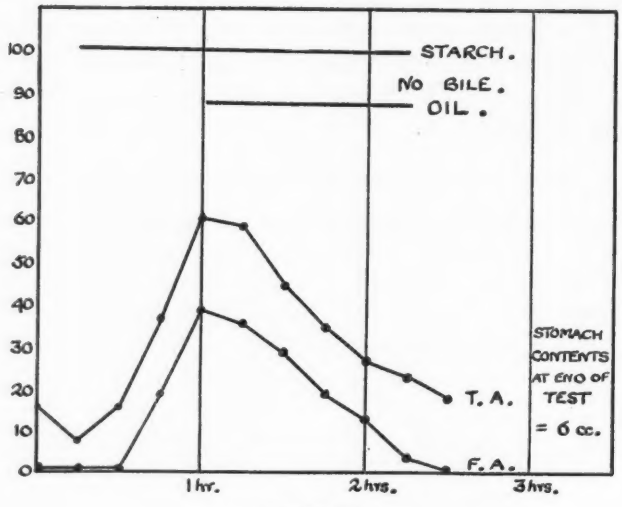

CHART 12.

Subject F. 1 oz. linseed oil through tube immediately before gruel.

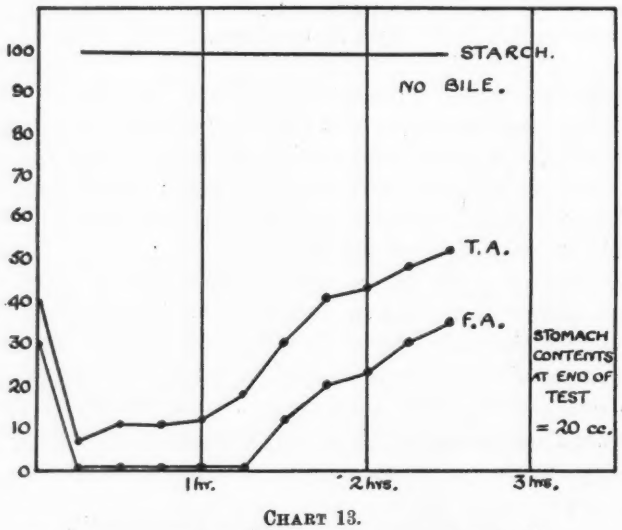

CHART 13.

Subject F. 1 oz. linseed oil through tube 20 minutes before gruel.

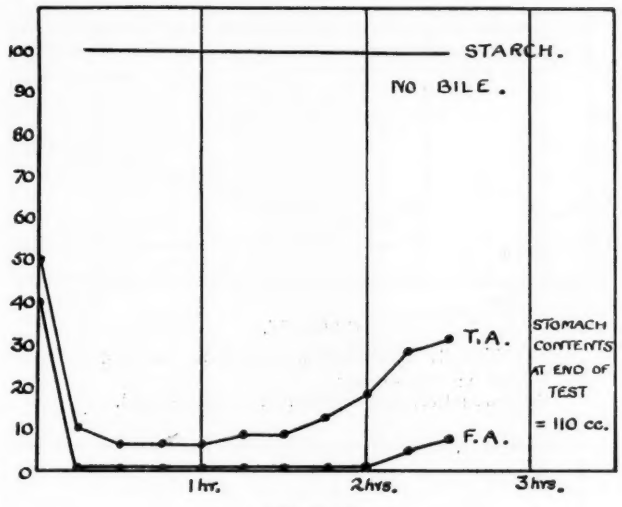

CHART 14.

Subject F. 1 oz. linseed oil through tube into duodenum immediately before gruel.

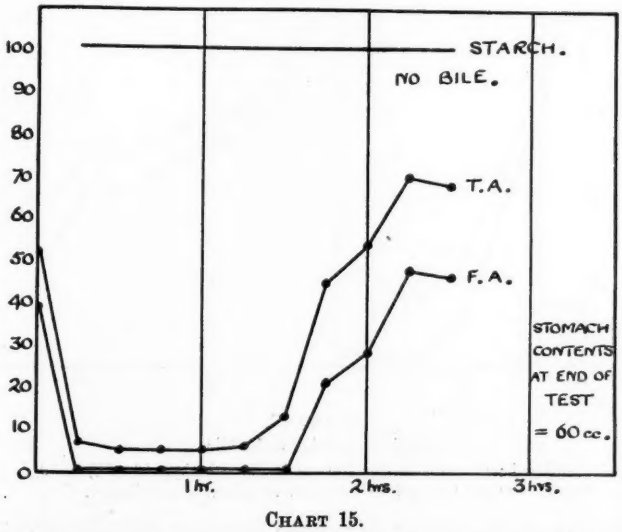

CHART 15.

Subject F. 1 oz. linseed oil emulsified with sodium oleate into duodenum immediately before gruel.

left the stomach within half an hour, yielded gruel samples for one and a half to two and a half hours (Chart 16).

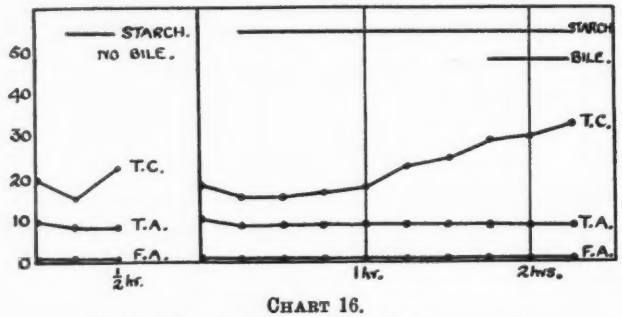

CHART 16.

Subject G. Achlorhydria (pernicious anaemia).
Section 1: Control meal.
Section 2: 1 oz. olive oil 10 minutes before gruel.

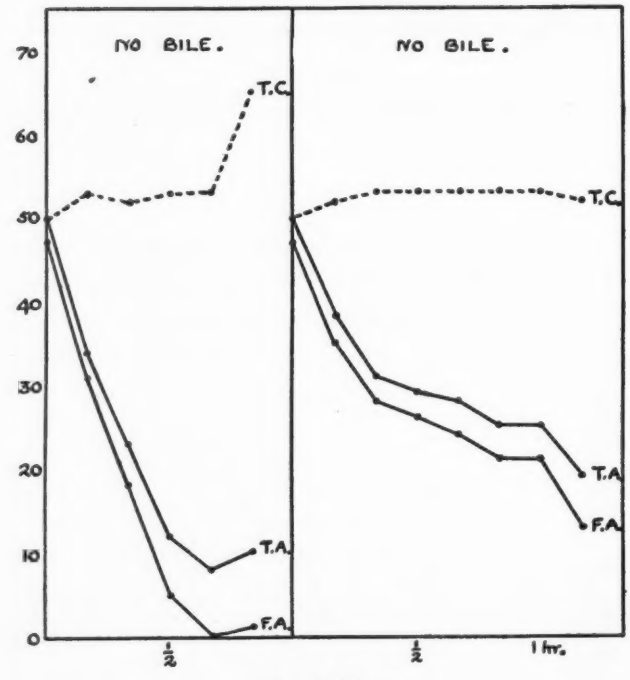

CHART 17.
Subject H. Achlorhydria.
Section 1: Control, using 500 c.c. hydrochloric acid of T.A. 50.
Section 2: As 1, but 1 oz. olive oil 10 minutes previously.

Achlorhydric cases generally show some degree of chloride secretion, which is reflected on the chart as a gradual rise in the total chloride curve. This chloride secretion was largely responsible for the fall in acidity observed in

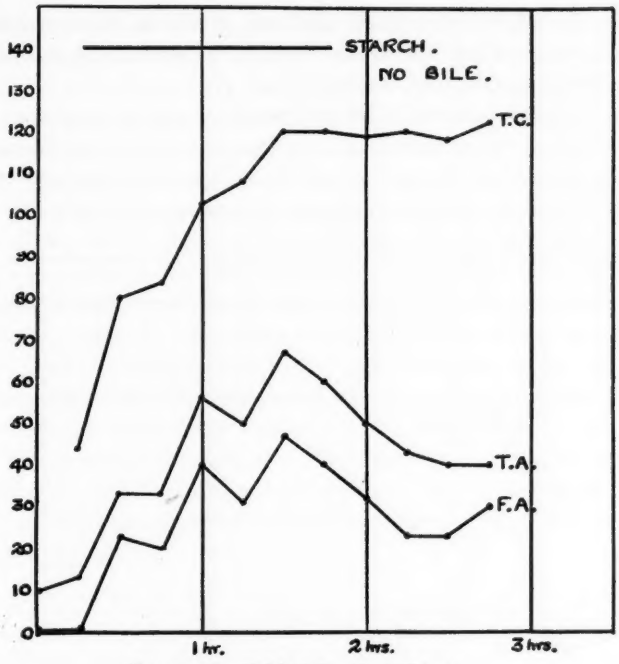

CHART 18. Subject J. Control test.

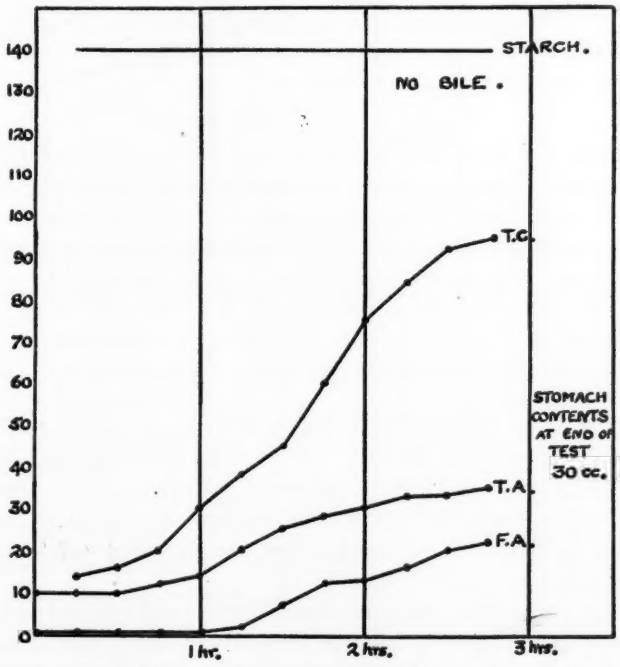

CHART 19. Subject J. 1 oz. linseed oil through tube 20 minutes before gruel.

several cases in which hydrochloric acid was given, as demonstrated by the creatinine method already described. Oil was found to inhibit this chloride secretion whilst decreasing the motility (Chart 17).

It is customary to prescribe hydrochloric acid in achlorhydria in the interests of gastric antisepsis; it would therefore appear advantageous to precede this by the administration of oil, in order to prolong the time that the acid remains in the stomach whilst minimizing its dilution by neutral chloride.

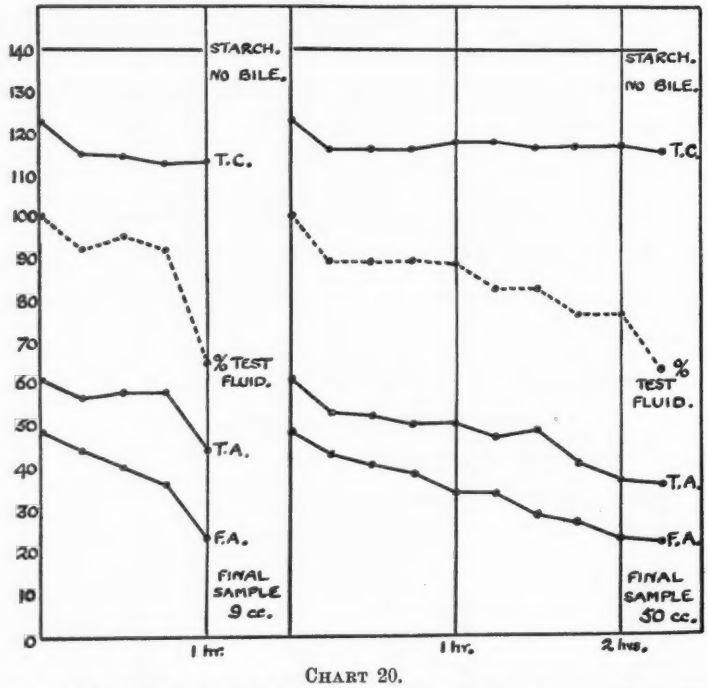

CHART 20.

Subject J. Section 1: Control test, using 500 c.c. mixture of composition: T.C. 123; T.A. 61; F.A. 49.
Section 2: As 1, but 1 oz. linseed oil through tube 20 minutes previously.

VI. *The Effect of Oil on Gastric Motility.*

It is clear that the lower acidity following oil is not merely a result of the delayed emptying, but the possibility requires to be considered that the delayed emptying may be secondary to the diminished secretion. If the stomach does not empty until a certain acidity or ionic concentration of its contents is reached, as suggested by Apperly (1926) and others, the emptying will necessarily be delayed when the secretion is inhibited.

The point was investigated as follows. The free and total acidities, chloride concentration, and the gruel percentage (creatinine method) were determined on a sample of gastric contents at a point towards the end of a meal when emptying

was in full progress. A mixture was then made up of similar composition and used in place of gruel in the next tests. As expected, the stomach emptied much more rapidly than in the control test, since there was no occasion for the retention of the meal for adjustment of acidity, &c. A further test was then given, using a second volume of the same test fluid, but preceded by the administration of oil. A delay in emptying resulted, which was almost as pronounced as when oil was given before the ordinary gruel meal (Charts 18 to 20). A consideration of the various curves in Chart 20 shows that a very slight neutralization of acid is occurring and that the stomach contents are being slowly diluted by a chloride secretion of concentration about 115. No secretion of hydrochloric acid of significance is occurring in either section of the test, which confirms MacLean's observation that hydrochloric acid of suitable concentration prevents the secretion of further acid by the gastric cells (1928). The results described above indicate quite clearly that the effect of oil on motility is not secondary to its effect on secretion. The effect of oil in achlorhydria, affords further evidence for the same conclusion; thus, Chart 16 shows the inhibition of motility although no appreciable secretion of chloride ion, either in the control or the oil test, took place.

Discussion.

A satisfactory theory of the effect of oils on gastric function will need to explain:

1. the inhibition of the psychical secretion
2. „ „ „ „ chemical „
3. „ „ „ „ chloride „
4. „ decrease of motility.

The inhibition of the chemical secretion by oil may be accounted for by the assumption that it prevents or delays the absorption of the substance or substances responsible. This, however, is insufficient to account for the inhibition of the psychical secretion and for the diminished motility. From the facts which have been collected at this stage of the investigation it seems necessary to assume either that the oil after absorption exerts some restraining influence on the gastric cells and the motility, or that it leads to the formation or liberation of some substance which acts in a similar manner. This latter type of alternative is favoured by Feng, Hou, and Lim, who suggest as a result of animal experiments that fat in the intestine leads to the formation of a 'chalone' for gastric secretion.

The chloride secretion proceeds simultaneously with the acid secretion and is in MacLean's view (1928), essentially the same process, so that this proposed explanation of the inhibition of acid applies equally well to the inhibition of chloride. The chloride secretion in achlorhydria is probably an expression of the same secretory process, and its inhibition may be accounted for in the same way.

Since the effect of oil is produced mainly or entirely after it has left the stomach, the order of efficiency of the oils described in Section I of this paper may represent the facility with which they pass from the stomach into the duodenum, in which case the order will be no longer maintained on their direct introduction into the duodenum down the tube. This point remains to be tested. In this connexion a recent observation of Tangl and Berend (1930) is of interest. They found that fat is converted in the small intestine by desaturation into water-soluble compounds which are dialysable and can then be absorbed. If this observation should be confirmed another explanation of the greater inhibitory efficiency of the less saturated oils will be available.

Summary.

1. The efficiency of oils in inhibiting gastric secretion appears to bear some relationship to the degree of saturation of the constituent fatty acids, the less saturated oils being the more efficient. The relationship between efficiency on the one hand, and specific gravity and viscosity on the other hand, is of less significance. Of related substances, only the free fatty acids show inhibitory properties.

2. Oil diminishes the response of the stomach to the presence of food and other stimulatory substances within it, but secretion due to histamine is not inhibited.

3. Oil inhibits both the psychical and the chemical secretions.

4. The action of oil is exerted mostly or entirely after it has left the stomach.

5. Oil diminishes the motility in cases of achlorhydria.

6. The effect of oil on gastric motility is not secondary to its effect on secretion.

7. The above facts are discussed, and a theory advanced of the action of oil on gastric secretion and motility.

I am indebted to Professor E. Mellanby for valuable criticism in the preparation of this paper, and to the Medical Research Council for a grant.

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THE CLINICAL INTERPRETATION OF THE INTRADERMAL TUBERCULIN REACTION[1]

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For many years investigators have striven to evolve some sort of 'test' which would help in the diagnosis of tuberculosis. Various methods of employing different varieties of tuberculin for this purpose have been popular from time to time and much literature has accumulated, particularly as regards the skin-test associated with the name of von Pirquet, with the net result that the bed-side use of this test has been discontinued in many centres. The intradermal use of tuberculin, as introduced by Mendel (1) and Mantoux (2) has very largely taken the place held by the von Pirquet test twenty years ago and there is a prevalent tendency to give it a diagnostic importance which is not really warranted on the evidence. Nearly all the published studies dealing with the Mantoux test describe a collection of several hundred cases, both children and adults, which are first divided into those showing positive and those showing negative results and each of these is further subdivided into such groups as 'proven tuberculosis', 'almost certainly tuberculosis', 'no evidence of tuberculosis', &c., or, as in another paper, a miscellaneous group of tuberculous patients, adults and children, pulmonary and non-pulmonary, is compared with a group of so-called 'healthy subjects' as regards their tuberculin reactions. Good examples of such 'tuberculin surveys' may be found in papers by Happ and Casparis (3), Elliott (4), Burhans (5), and Cummins (6), but each of these studies has the fundamental disadvantage that while many important facts about the scientific meaning of the intradermal tuberculin test emerge the application of these facts for diagnostic purpose to the *individual* case at the bed-side is dealt with in brief and often vague generalizations. For this reason it has been felt that a more clinical study of the Mantoux reaction was desirable, and in the present paper an attempt is made to discuss the results of intradermal tuberculin reactions as they appear to the observer at the bed-side, faced with some problem in diagnosis. The subject is not easy to present in this way for the very reason that such a clinical study almost requires a discussion of each individual case where the tuberculin test was used, and unless a reasonable number of cases are described no deductions would be valid. As far as

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possible the statistical aspect is neglected here, although figures have to be used in the description of the material.

An ideal 'test' for tuberculosis should be simple to perform, preferably at one sitting, with an easily attainable degree of accuracy, it should be devoid of all harm for the patient and the results should be easy to read and interpret. No such test at present exists, but the Mantoux reaction certainly comes nearest to this ideal except as regards the question of interpretation. That it has advantages over the von Pirquet reaction is fairly obvious, for in the intradermal test an accurately measured dose of tuberculin is delivered *into* the skin while in the von Pirquet test the amount of tuberculin getting into the skin depends upon the degree of scarification and other variable factors. Various workers have compared these two tests and papers by Bass (7), Krogsgaard (8), and Burhans (5) give comparative studies. It is estimated that the average dose in the von Pirquet test is about 0·01 mg. of old tuberculin. The usual dose in the Mantoux test is about ten times this and most workers are agreed that a certain number of positive reactions to the Mantoux test would be negative to the smaller dose employed in the von Pirquet reaction, so that the intradermal method is less likely to miss tuberculous cases.

This paper is not concerned with the exact nature of the intradermal reaction and it is accepted that the positive response is an allergic phenomenon indicating that the patient has become hypersensitive to tuberculin, probably as a result of infection with tubercle bacilli.

Zinsser (9) or Tytler (10) should be consulted for a modern summing-up of this aspect of the problem. It is probable that a positive reaction develops in man about three weeks to three months after infection (Burhans).

Method.

Certain of the fallacies in the interpretation of the intradermal tuberculin test can be attributed to faulty technique, so that strict attention to detail is necessary. Nevertheless for the test to be of any practical value simplicity in method must be aimed at.

An all-glass syringe, with an accurately fitting piston and graduated in tenths of a cubic centimetre, is required with a supply of well-fitting hypodermic needles which should be kept sharp. Where large numbers of controlled tests are being performed it is an advantage to have a second syringe for the control solution, but if isolated cases are being tested this is not necessary as long as the control solution is used before the tuberculin solution and never vice versa; the syringe should be washed in saline between the two injections. The tuberculin used in the present series was not a special batch (as with many of the published investigations) but ordinary stock 'Koch's old tuberculin' obtained as required from Messrs. Burroughs Wellcome & Company. Most of the work was done with human tuberculin, but where bovine tuberculin was used it came from the same source as did also the control solution consisting of

glycerine-veal broth. The tuberculin was diluted in the laboratory in stock solutions of 1 in 10, 1 in 100, 1 in 1,000, and 1 in 10,000. These solutions contained 10 mg., 1 mg., 0·1 mg., 0·01 mg. of old tuberculin respectively in the standard dose of 0·1 c.c. Dilution was carried out freshly about once a fortnight, the solutions being kept in the laboratory ice-chest and supplied to the wards as required. The control solution was diluted in the same way, 0·5 per cent. carbolic-saline being used.

The control solution, when used, and the tuberculin were injected into the patient in the following way:

The palmar surface of the forearm is rubbed with a swab soaked in ether and dried with a dry swab. The skin is then stretched tight with the left hand while the needle and syringe are held in the right hand. The needle is introduced *into* the skin for about five to ten millimetres, great care being taken to see that the needle is really in and not under the skin. The dose of control solution or of tuberculin, in all cases 0·1 c.c., is then injected and should raise a small wheal. It is convenient to inject the control into one arm and the tuberculin into the other. The arms are examined daily for any reaction, but as a matter of experience the maximum result in positive cases occurs in forty-eight hours and consists of a red area of swelling, easily palpable, frequently tender and of an average diameter of about two centimetres. Around this is a variable area of erythema, but erythema alone without a palpable swelling is not sufficient for a test to be called even faintly positive. The control reactions when positive are similar as regards swelling and erythema.

The tests in the present series were jointly carried out by house-physicians or by myself, while a certain number were done by Dr. Janet Young working in Dr. Robert Hutchison's ward. In each instance when the test was carried out by some one else the results were also read by me, and if there appeared to be any doubt about a reaction the test was repeated. The clinical condition of every patient here dealt with and the progress of the cases were personally noted by me. I am greatly indebted to all those who have assisted me in the practical side of this investigation.

Material Used and Results.

During the twelve months, July 1928 to June 1929 inclusive, a total of 206 patients in the medical wards of the Hospital for Sick Children, Great Ormond Street, were submitted to the intradermal tuberculin reaction. The patients were of all ages, from a few weeks to twelve years, and were suffering from various complaints as indicated in the tables to be given later. No attempt has been made to follow up these patients after their leaving hospital, as the sole purpose of this paper is the use of the Mantoux test at the bed-side, and the diagnosis given for each case is the final diagnosis arrived at in hospital with all the information available. It is possible that subsequent progress might show this diagnosis to be incorrect in certain cases, and when the

Mantoux test was inexplicably positive, for example, later information might have proved that tuberculosis was at the root of the patient's illness. The present investigation is not, however, concerned with this particular point.

Of the 206 patients, 88 were deliberately selected as control cases. That is to say, the Mantoux test was done without any idea of seeking for information about the nature of the illness for which the patient was in hospital. Patients were selected when tuberculosis was a most unlikely cause of their symptoms. In the remaining 118 cases the tuberculin test was employed as one of the methods available in establishing a diagnosis. The control group of cases will be discussed first and the 'diagnostic' group later.

Control Cases.

A full list of control cases arranged in age-order is given in an appendix. Human tuberculin was used throughout this group always in the standard dose of 0·1 c.c. of whatever solution was being used. The youngest patient in the series was four weeks and the oldest twelve years. Of these 76 were negative to intradermal tuberculin, while 12 were positive. It is interesting to observe that positive reactions do not appear in the series until after seven years of age, and the 12 positive reactions occurred amongst 55 patients of seven years or more. Of the 76 negative cases, 70 were negative to one injection of 0·1 mg. of tuberculin and of these 12 were also negative to a control solution. Two patients were negative to 0·1 mg. and 1 mg. of tuberculin, one to 1 mg. and 0·2 mg. of tuberculin, and three to three doses of tuberculin, 0·01 mg., 0·1 mg., 1 mg. in two instances with 0·1 mg., 0·2 mg., and 1 mg. as the dosage in the third case. None of these six patients was given a control injection.

There is very little to comment upon these negative results, except to point out that repeated doses of tuberculin at short intervals do not sensitize a patient to tuberculin as has been suggested. If this were so then the 1 mg. doses coming as long as two to three weeks after the initial dose of, say 0·01 mg. might produce a positive result where previous doses had been negative. This certainly happened in two of the present control patients, but Calmette (11) states that while such sensitization may occur in an already infected individual, it never happens in a person free from tuberculosis. Bass (7) injected 1 mg. of tuberculin every other day for fourteen days into the skin of a healthy infant without producing any reaction.

The twelve 'positive' cases in this control group raise several interesting points for discussion. In eight instances a positive result with both 0·1 mg. of old tuberculin and the control solution was obtained; this was repeated in several instances since such results were somewhat surprising. In none of these patients was there any evidence that the disease from which the child was suffering was tuberculosis, nor was there any explanation forthcoming from the child's general condition for the positive reaction with the control solution. In a study especially concerned with the use of controls in the intradermal tuber-

culin reaction, Heise and Brown (12) tested tuberculous patients with glycerin-bouillon and found that approximately 4 per cent. of these patients reacted positively both to tuberculin and to glycerin-bouillon solution.

It has been suggested by Dolter (13) that in some patients where positive reactions with control solutions occur, the meat used in preparing the bouillon may have come from tuberculous animals. This is very unlikely to have happened in the present series, but it is mentioned here to emphasize the possibility of experimental error in even such a simple procedure as the intradermal tuberculin test. Of the eight patients with positive reactions to the control solution, five occurred in one ward at the same period of the investigation, which suggests that some mistake may have been made. Possible errors which lead to such fallacious results include faults in manufacture, careless dilution, lack of care in the ward, use of contaminated syringe or needles, &c. It is not suggested that any of these errors necessarily occurred in the present series, but the list is given as a warning that even control solutions must be controlled. Probably a control injection should always be used when the tuberculin test is done, but this ideal was certainly not attained in this series.

In the remaining four positive patients no control was used, and the results of such a small number must not be stressed. It is curious that two of these patients should have been negative to a smaller and positive to a larger dose of tuberculin. In neither instance was the child very ill nor was there any suspicion of tuberculosis about the patient's illness or progress. In view of Calmette's comments on sensitization by tuberculin it is possible that both these patients had been already infected with tuberculosis. A case of pericarditis positive to 0·01 mg. and 0·1 mg. caused great difficulty in diagnosis and it is possible that the process was tuberculous.

A general survey of the control group of cases suggests that a positive reaction to tuberculin occurring in the second half of childhood has not the same significance as a positive result at an earlier age unless properly controlled. This is discussed more fully later. More work is needed on the subject of control reactions, for there appears to be a small number of children giving a positive skin reaction to glycerin-veal broth and thus invalidating the tuberculin test.

'*Diagnostic Results.*'

The 118 cases where tuberculin was used as one of the means of diagnosis have been arranged according to the region of the body affected or the type of illness present. As in the control group the diagnosis given is the final diagnosis established on general considerations at the end of the patient's stay in hospital. In some instances it may be that subsequent information would have led to some modification, but for the purposes of this study the clinical diagnosis will be the basis of any discussion. These 118 cases fall into eight groups: chest

conditions, abdominal conditions, intracranial conditions, obscure fevers, enlarged glands, kidney affections, bone conditions, and a miscellaneous group. It is proposed to present the results of the tuberculin tests in tabular form and discuss each group in turn in order to bring out the usefulness or otherwise of the intradermal tuberculin reaction.

TABLE I. *Chest Conditions.*

Standard dose of 0·1 c.c. tuberculin solution used in each case. Control results not tabulated.

Initials.	Sex.	Age. yrs.	Age. mos.	Final Diagnosis.	Results with Tuberculin. 0·01 mg.	0·1 mg.	1 mg.	Remarks.
J. C.	M	—	5	Tuberculous pneumonia	—	pos.	—	Proved *post mortem*
J. W.	M	—	8	Broncho-pneumonia	—	neg.	—	
S. P.	M	—	10	Bronchitis	—	neg.	—	
R. H.	M	1	1	Pulmonary fibrosis	—	neg.	—	Also neg. to 0·2 mg.
M. C.	F	1	2	Bronchitis	—	neg.	—	
J. A.	F	1	2	Apical pneumonia	—	pos.	—	
D. H.	F	1	3	Empyema	—	pos.	—	Streptococcal case
J. W.	M	1	4	Chronic pneumonia	neg.	neg.	neg.	
N. D.	M	1	6	Bronchitis	—	neg.	—	
B. C.	F	1	6	Pneumonia	—	neg.	—	
A. T.	M	1	6	Pulmonary tuberculosis	—	pos.	—	Died
G. B.	M	1	9	Apical pneumonia	—	pos.	—	
V. C.	F	2	1	Pulmonary tuberculosis	—	pos.	—	T.B. in sputum
P. D.	M	2	2	Pulmonary fibrosis	—	neg.	—	
J. B.	M	2	5	Bronchitis	—	pos.	—	
S. W.	M	2	8	Broncho-pneumonia	—	neg.	—	Died
S. C.	M	3	—	Asthma	—	neg.	—	Also neg. to 0·2 mg.
J. B.	M	3	—	Apical pneumonia	—	pos.	—	
H. C.	M	3	—	Pulmonary fibrosis	—	pos.	—	
T. C.	M	4	—	Pneumonia	—	neg.	—	
W. K.	M	4	—	Bronchitis	—	pos.	—	
B. L.	F	4	—	Tuberculous pneumonia	—	neg.	—	Proved *post mortem*
C. L.	M	4	3	Pleural effusion	—	pos.	—	
E. D.	F	5	—	Pulmonary fibrosis	—	neg.	—	
M. B.	M	5	—	Bronchitis	—	neg.	—	
S. W.	M	5	6	Bronchitis	—	neg.	—	
W. C.	F	5	6	Pulmonary fibrosis	—	—	pos.	
W. C.	F	5	6	Pulmonary fibrosis	—	neg.	—	Also neg. to 0·2 mg.
R. S.	M	5	9	Pulmonary fibrosis	—	pos.	—	
H. S.	M	6	1	Empyema	—	neg.	neg.	
J. N.	F	7	—	Pulmonary fibrosis	—	neg.	neg.	
D. R.	F	7	9	Mediastinal glands	—	pos.	—	

TABLE I (*continued*).

Initials.	Sex.	Age. yrs.	Age. mos.	Final Diagnosis.	Results with Tuberculin. 0·01 mg.	0·1 mg.	1 mg.	Remarks.
G. D.	M	8	—	Thickened pleura	—	neg.	—	
M. A.	F	8	1	Pulmonary fibrosis	—	neg.	—	
E. H.	F	8	2	Bronchiectasis	—	neg.	—	
K. H.	M	8	4	Lymphadenoma	—	pos.	—	Mediastinal tumour
H. H.	F	8	6	Pulmonary tuberculosis	—	pos.	—	T.B. in sputum
N. O.	M	9	—	Asthma	—	neg.	—	
C. A.	M	9	—	Pulmonary fibrosis	—	neg.	—	
A. A.	M	9	6	Unresolved pneumonia	—	—	pos.	Good recovery
J. C.	M	10	—	Bronchiectasis	—	neg.	—	
A. H.	M	10	9	Pulmonary tuberculosis	—	pos.	—	Pos. to bovine also
I. A.	M	11	—	Pulmonary tuberculosis	—	pos.	—	
R. C.	F	11	—	Pleural effusion	—	pos.	—	

This group of forty-four cases of disease within the thorax is the largest of the eight. It will be seen that the usual dose of 0·1 mg. of human old tuberculin was employed and in certain cases additional doses of 0·01 mg., 0·2 mg. or 1 mg. were used. Records of the results of the injection of control solution are not given in these tables, as in the few instances where this was done a negative result was usually obtained, so that the positive readings with tuberculin can be accepted for the most part as true positives. The exceptions are noted in subsequent comments.

Of the forty-four cases, seven were examples of pulmonary tuberculosis either in an acute broncho-pneumonic form or as the adult type of fibro-caseous phthisis. Six of these patients were positive to tuberculin and the seventh was negative in a very ill child. This question of acute tuberculous conditions and negative readings will be more fully discussed in connexion with the febrile group of cases. Two examples of serous pleural effusion were positive to 0·1 mg. of tuberculin, but so was a case of streptococcal empyema in a child just over one year of age. The empyema was drained and the infant made a complete recovery, never exhibiting any symptoms which could be attributed to tuberculous infection. Another example of empyema due to the pneumococcus was negative. Fifteen cases in this group came under the heading of chronic non-tuberculous lung infection, being examples of unresolved pneumonia, pulmonary fibrosis, thickened pleura or bronchiectasis. In all these cases the clinical evidence was strongly against tuberculosis yet four cases gave positive tuberculin reactions. All these cases ran the course of non-tuberculous cases and the positive tuberculin test merely obscured both the diagnosis and prognosis. In the remaining eleven cases of pulmonary fibrosis the negative result was helpful in excluding tuberculosis, especially where a child was negative to both 0·1 mg. and 1 mg. in two doses at about a week's interval.

Seven cases of pneumonia gave interesting results. Two very ill infants with broncho-pneumonia were negative and died, no tuberculosis being found *post mortem*. Two straightforward lower lobe pneumonias were negative and made good recoveries. The remaining three were upper lobe pneumonias, mild in type but all very slow to resolve and all three children were positive to 0·1 mg. of tuberculin. The ages of these children were fourteen months, twenty-one months, and three years, and the association of a mild pneumonic process in the upper lobe with a positive tuberculin test at this early age suggests that these three cases fall into the interesting group of so-called 'epi-tuberculosis' (Eliasberg and Neuland) (14). It is outside the province of this paper to discuss this condition, but the net result of the tuberculin tests in pneumonia would seem to be that where positive it by no means necessitates a gloomy prognosis and where negative it does not necessarily exclude tuberculosis if the usual dose of 0·1 mg. alone is employed, as will be explained when the miliary tuberculosis cases are discussed.

There remain two cases of asthma, both negative, and seven cases of bronchitis where two positive results were obtained in children aged 2½ and 4 years, both given 0·1 mg. of tuberculin. Both these patients ran the ordinary course of an acute bronchitis and made good recoveries, so that the tuberculin test was most deceptive and had to be ignored in making a prognosis.

The two other cases of this group both raise points for discussion. One was an example of enlarged mediastinal glands where a positive result to 0·1 mg. of tuberculin was obtained. Since this investigation is concerned entirely with in-patient cases further examples of this type of case are not available and so no generalizations are possible. In this particular patient, however, X-ray examination gave no support to the diagnosis of tuberculous enlargement of the mediastinal glands, and it would seem that a positive tuberculin test ought not to be allowed to influence the diagnosis in such cases. The example of the last patient in this group of chest cases must be strongly emphasized as illustrating one of the fundamental fallacies of all tuberculin tests. Here a boy of eight-and-a-half years died with a large mass in his anterior mediastinum. He had given a positive reaction to 0·1 mg. of tuberculin, but the autopsy showed that it was due to a small caseous gland in his mesentery while the mass in the chest consisted of lymphadenoma and was not tuberculous at all. In other words, this case illustrates that a positive tuberculin test is only evidence of tuberculous infection somewhere in the body and does not necessarily indicate that the disease from which the patient is suffering is tuberculous. This is also illustrated by two of the cerebral tumour cases in group 3.

Twelve of these twenty-three abdominal cases (Table II) suffered from some form of abdominal tuberculosis; nine gave positive tuberculin reactions. The diagnosis of one of the three negative cases was doubtful, but the other two were definite clinically and neither patient was febrile nor very ill. Both of these were tested only with human tuberculin and this raises the question whether bovine tuberculin should also be used, especially in abdominal cases.

In this series bovine tuberculin has been very seldom used and there was no case positive to bovine and negative to human tuberculin. Burhans (5) believes that practically all tuberculous patients will react to either type of tuberculin provided that large enough doses are employed. Tisdall and Brown (15) in a series of 159 cases never found an example positive to bovine tuberculin which was negative to human tuberculin. On the other hand Downing and

TABLE II. *Abdominal Conditions.*

Initials.	Sex.	Age. yrs.	Age. mos.	Final Diagnosis.	Results with Tuberculin. 0·01 mg.	0·1 mg.	1 mg.	Remarks.
J. M.	M	—	7	Coeliac disease	—	neg.	—	
J. T.	F	1	—	Abdominal tuberculosis	—	neg.	—	
E. G.	F	1	8	Abdominal tuberculosis	—	neg.	neg.	Doubtful case
D. B.	F	2	3	Abdominal tuberculosis	pos.	pos.	—	
W. S.	F	2	10	Abdominal tuberculosis	—	pos.	pos.	
E. B.	F	3	—	Coeliac disease	—	neg.	—	
B. H.	F	3	6	Coeliac disease	—	neg.	—	
E. S.	M	3	7	Suprarenal Sarcoma	—	neg.	—	
L. C.	F	3	7	Constipation	—	neg.	—	
D. S.	F	3	10	Coeliac disease	—	neg.	neg.	Neg. also to bovine and control
P. S.	F	4	—	Constipation	—	neg.	—	
D. B.	M	4	—	Coeliac disease	—	neg.	—	
J. K.	F	4	—	Abdominal tuberculosis	—	pos.	—	
D. A.	M	4	—	Coeliac disease	—	neg.	—	Neg. also to bovine
G. S.	M	4	8	Abdominal tuberculosis	—	pos.	—	
A. B.	M	5	—	Abdominal tuberculosis	—	neg.	—	
D. S.	M	5	6	Abdominal tuberculosis	—	—	—	Pos. to 0·2 mg.
M. C.	F	6	6	Abdominal tuberculosis	—	pos.	—	
L. L.	M	6	10	Suprarenal sarcoma	—	neg.	—	
K. H.	M	7	6	Abdominal tuberculosis	—	pos.	—	
G. H.	F	8	—	Perinephric abscess	—	neg.	—	
A. P.	M	8	5	Abdominal tuberculosis	—	pos.	—	
V. G.	F	11	—	Abdominal tuberculosis	—	neg.	pos.	Very ill child

Higgins (16) in a group of fifty-one patients with tuberculosis found eight giving positive reactions to bovine tuberculin intradermally while they were negative to human tuberculin, and they conclude that there is a possible error of 16 per cent. unless both tuberculins are used for routine testing. This is probably an exaggeration of the risk and as a working rule, since investigators seem to be divided in opinion upon this point, bovine tuberculin need only be used after repeated negative results with human tuberculin in a difficult case, especially in abdominal, bone, or gland conditions.

In the six cases of coeliac disease in this group the diagnosis was very difficult in two and bovine tuberculin also gave negative results. In one of these patients where the abdomen had actually been opened at another hospital for tuberculous peritonitis several doses of tuberculin, both human and bovine, (0·1 mg. and 1 mg. of each) failed to give positive results and at a post-mortem examination many weeks later there was no trace of tuberculosis anywhere in the body. The remaining cases, constipation (2), suprarenal sarcoma (2), and perinephric abscess (1) were all negative to tuberculin and the test appeared to be of help in excluding tuberculosis in such cases.

TABLE III. *Intracranial Conditions.*

Initials.	Sex.	Age. yrs.	Age. mos.	Final Diagnosis.	Results with Tuberculin. 0·01 mg.	0·1 mg.	1 mg.	Remarks.
A. S.	F	—	4	Tuberculous meningitis	—	pos.	—	
D. O.	M	—	6	Encephalitis	—	neg.	neg.	
L. L.	F	—	8	Tuberculous meningitis	—	pos.	—	
D. L.	F	—	9	Hydrocephalus	—	neg.	—	
P. M.	M	—	10	Meningococcal meningitis	—	neg.	—	
D. W.	M	1	3	Mental deficiency	—	pos.	—	
J. T.	F	1	6	Cerebral tumour	—	neg.	—	
B. S.	F	1	10	Tuberculous meningitis	—	neg.	—	
K. G.	M	2	—	Meningococcal meningitis	—	neg.	—	
H. B.	M	2	8	Cerebral tumour	—	pos.	—	Test repeated twice
T. W.	M	3	3	Meningococcal meningitis	—	neg.	—	
J. F.	F	6	6	Tuberculous meningitis	—	neg.	—	
W. A.	M	7	9	Cerebellar tumour	—	neg.	—	
D. H.	M	8	10	Cerebral tumour	—	pos.	—	
G. H.	F	10	6	Cerebral tumour	—	neg.	—	
H. B.	M	10	6	Cerebral tumour	—	neg.	—	

The sixteen examples of intracranial disease produced some interesting results. Of the four cases of tuberculous meningitis two were faintly positive to 0·1 mg. of tuberculin and two were negative. This feature of acute tuberculous conditions is discussed more fully in connexion with the next group of febrile disorders, but in passing it may be said that negative results with 0·1 mg. of tuberculin in meningococcal meningitis cases are of no help in excluding tuberculosis pending the result of examination of the cerebrospinal fluid, and it would probably be better to use 1 mg. straightaway in all meningitis cases.

Among the six cases of intracranial tumour, two gave a positive reaction to tuberculin, and in neither instance was the tumour tuberculous. In one of these cases, a boy of two and a half years, a positive result was obtained to 0·1 mg. of tuberculin on two occasions, but *post mortem* no trace of any tuberculosis could be found anywhere in the body. In the other case, a boy of nine years,

examination of the head only was permitted *post mortem*, so that the cause of the positive tuberculin test could not be ascertained. It would seem that as far as intracranial tumours are concerned the results of tuberculin tests must be ignored, for a diagnosis of tuberculosis based upon a positive test in these two cases would have been quite incorrect and might, in other instances, lead to the adoption of the wrong type of treatment. These cases again illustrate that a positive tuberculin reaction does not mean that the child's condition is necessarily due to tuberculosis.

The other three cases in this group do not require any comment.

TABLE IV. *Febrile Conditions.*

Initials.	Sex.	Age. yrs.	Age. mos.	Final Diagnosis.	Results with Tuberculin. 0·01 mg.	0·1 mg.	1 mg.	Remarks.
T. B.	M	—	4	Miliary tuberculosis	—	neg.	—	Moribund
E. B.	F	2	6	Miliary tuberculosis	—	pos.	—	
M. W.	F	3	10	Paratyphoid fever	—	pos.	—	Strongly pos. result
R. C.	F	4	—	Miliary tuberculosis	—	pos.	—	
H. B.	F	4	10	Pyrexia—cause?	—	neg.	—	
W. C.	F	7	—	Pyrexia—cause?	—	neg.	neg.	
I. M.	M	7	6	Septicaemia	—	neg.	—	
F. F.	M	10	—	Influenza	—	neg.	—	
D. W.	M	10	—	Pyrexia—cause?	—	pos.	—	

In febrile states the interpretation of the tuberculin test becomes even more difficult than in non-febrile conditions. Several workers have shown that it is almost always possible to obtain a positive result in an acute case of tuberculosis provided a large enough dose of tuberculin is given. Happ and Casparis (3), for example, showed this quite definitely with the increasing doses they employed and obtained 100 per cent. positive results when the amount of tuberculin was over 1 mg. The danger of sensitization by repeated doses of tuberculin has already been discussed and dismissed as of no practical importance. In acute tuberculosis the child's allergic response is depressed and more tuberculin is necessary to obtain a positive result. Now if the usual dose of 0·1 mg. or even 0·01 mg. is given first and then, after about a week, the result is considered negative, the next highest dose is given and so on, the chances are that an ill child will not live long enough for the tests to be completed. In the three cases of miliary tuberculosis in this series one was strongly positive, one faintly positive, and one negative to 0·1 mg. of tuberculin. It might be wise in these very ill patients to give at least 1 mg. at once instead of the smaller doses on the grounds that if the condition is generalized tuberculosis no additional harm can result and, if not, then the reaction will be negative. This only applies in the first two years of life.

It will be seen in the above table that one patient suffering from obscure pyrexia, discharged cured, and one with paratyphoid fever were both positive to 0·1 mg. of tuberculin. In neither case had this result any bearing on the cause of the fever, but it puts the question whether a positive result to a small dose of tuberculin in an ill and feverish child might not, paradoxically, be almost as likely to exclude tuberculosis as the cause of the fever as to indicate it. These observations on the small doses of tuberculin in acute cases apply also to cases of pneumonia and of meningitis mentioned above.

TABLE V. *Enlarged Glands.*

Initials.	Sex.	Age. yrs.	Age. mos.	Final Diagnosis.	Results with Tuberculin. 0·01 mg.	0·1 mg.	1 mg.	Remarks.
G. R.	M	—	9	Lymphadenoma	—	neg.	neg.	
P. C.	M	—	9	Tuberculous glands	—	pos.	—	
A. W.	M	1	10	Septic glands	—	neg.	—	
W. A.	M	2	—	Streptococcal glands	—	neg.	—	
S. A.	M	2	—	Tuberculous glands	—	pos.	—	
G. B.	M	2	11	Tuberculous glands	—	pos.	—	
P. C.	M	4	—	Septic glands	—	neg.	neg.	
A. R.	M	4	9	? Nature of glands	—	neg.	neg.	Probably not tuberculous
G. W.	M	8	7	Tuberculous glands	—	pos.	—	

There is little to comment about these cases. In one of the patients giving a positive result the diagnosis was clinically doubtful and the tuberculin test helped. In the negative cases the question of tuberculosis only really arose in one case and the negative tuberculin test helped to exclude it. In connexion with these gland cases the example of lymphadenoma in the anterior mediastinum mentioned in group I should be remembered.

TABLE VI. *Kidney Affections.*

Initials.	Sex.	Age. yrs.	Age. mos.	Final Diagnosis.	Results with Tuberculin. 0·01 mg.	0·1 mg.	1 mg.	Remarks.
P. O.	F	2	9	Pyelitis	—	neg.	—	Proved not tuberculous
J. M.	F	3	—	Acute nephritis	—	pos.	—	
M. B.	M	4	—	Acute nephritis	—	neg.	—	
J. B.	M	4	—	Acute nephritis	neg.	neg.	neg.	
D. M.	F	5	6	Pyelitis	—	neg.	neg.	
R. S.	M	5	10	Acute nephritis	neg.	neg	neg.	
T. K.	F	6	—	Pyelitis	neg.	neg.	neg.	Haematuria
J. K.	F	9	—	Acute nephritis	—	pos.	—	Control positive

These eight examples of kidney disease fall into two groups. In five instances the degree of haematuria present led to some doubt being cast upon the diagnosis of acute nephritis although subsequent progress put all five cases definitely in the 'acute haemorrhagic nephritis' class. Despite this, two of the

five were positive to tuberculin, one of these cases being also strongly positive to the control solution. These positive results gave no help in diagnosis and had to be ignored. Both children recovered and were discharged well. The other group contained three cases of pyelitis where unusual chronicity made it important to exclude tuberculosis. Here the tuberculin reactions were all negative, in some cases after several doses, so that some help was afforded by the test. The several examples of repeated negatives to increasing doses of tuberculin should be noted.

TABLE VII. *Bone Affections.*

Initials.	Sex.	Age. yrs.	mos.	Final Diagnosis.	Results with Tuberculin. 0·01 mg.	0·1 mg.	1 mg.	Remarks.
R. U.	M	2	3	Spinal caries	—	neg.	neg.	Neg. also to 1 mg. bovine
G. W.	F	3	—	? Spinal caries	neg.	neg.	neg.	

It is to be regretted that there are not more examples of these 'surgical' types of tuberculosis in this present series, as they form a most important group where the value of tuberculin tests needs to be carefully ascertained. In one of the two cases here recorded all the clinical and X-ray evidence supported the diagnosis of tuberculosis, the child was not acutely ill and yet only negative tuberculin results, human and bovine, could be obtained.

TABLE VIII. *Miscellaneous.*

Initials.	Sex.	Age. yrs.	mos.	Final Diagnosis.	Results with Tuberculin. 0·01 mg.	0·1 mg.	1 mg.	Remarks.
H. H.	F	—	6	Polyarthritis	—	neg.	—	
F. P.	M	1	2	Laryngeal stridor	—	neg.	—	Control neg.
G. H.	M	3	9	Malnutrition	—	neg.	—	
L. D.	M	4	6	Toxic oedema	—	neg.	—	
L. D.	F	8	10	Erythema nodosum	—	—	pos.	Bullous response
F. L.	M	11	—	Erythema nodosum	—	pos.	—	Acute reaction
D. W.	F	12	—	Erythema nodosum	—	neg.	—	

There is very little to be said about this miscellaneous group except to point out the three cases of erythema nodosum, one of which was negative and the other two positive. Indeed, one of these positive cases, which was given an initial dose of 1 mg., had a most violent reaction with the formation of a large bullous area and a wide extent of erythema. This was the only case in the whole 206 where the reaction gave rise to more than slight discomfort.

General Summary and Discussion.

Many points have already been dealt with as they were suggested by the the analysis of case records, and in the general summing-up repetition will be

avoided as much as possible. A general survey of the 118 cases where tuberculin was expected to help in the diagnosis must lead to the conclusion that too much must not be expected of the Mantoux test, and that the instances where the test gives reliable and necessary help in diagnosis are limited in number. In many cases the test gave no help at all when it was needed, as, for example, is shown by the negative results in some instances of abdominal tuberculosis and the spinal caries case. In other patients a positive result had no bearing upon the disease from which the child was suffering, as with the two cases of cerebral tumour, and the lymphadenoma of the mediastinum. These three patients came to necropsy so that there was no doubt about the false nature of the information provided by the tuberculin test, but there were numerous other cases in the series where positive results occurred in a child whose disease was never at all like tuberculosis. Finally, at least one positive patient came to necropsy in which no evidence of tuberculosis could be found anywhere in the body.

Dr. Hugh Thursfield, for whose criticism and encouragement I am much indebted, has kindly permitted me to quote here his own experiences with tuberculin tests. His records extend over ten years and relate to 278 cases. Among these are 96 cases of suspected pulmonary tuberculosis, and 65 of these were negative to either the von Pirquet or Mantoux test, while 31 were positive. Of the negative cases 15 were positive to subcutaneous tuberculin (0·005 grm.) and of the positive cases 20 were positive with subcutaneous tuberculin. In this pulmonary group were included cases which, in Dr. Thursfield's opinion, were certainly not tuberculous, but it is interesting to note that in 15 patients among the more suspicious a subcutaneous reaction was positive against a negative von Pirquet or Mantoux reaction. In a group of abdominal cases 13 were positive and 7 were negative to the tuberculin skin test, of tuberculous meningitis 2 were positive and 6 negative, and of generalized tuberculosis 5 were positive and 4 negative. Thus in these three groups, totalling 37 cases in all, the skin reaction gave correct information in 20 instances and was incorrect in 17.

The value of the intradermal tuberculin test can best be summed up under two headings: the value of a negative reaction and the value of a positive reaction.

(*a*) The value of a negative reaction is reduced by the possibilities of several fallacies, all of which have already been mentioned. The tuberculin used may not be potent, the injection may be made subcutaneously instead of intradermally, the patient may fall into the small group where bovine tuberculin is necessary to obtain a positive result and is negative with human tuberculin, or finally, the patient may be in such a state of acute tuberculosis or of some acute illness not due to tuberculosis (such as measles) that a negative result is obtained with ordinary doses of tuberculin. All these positive dangers connected with negative results with tuberculin are comparatively easy to combat by careful work, but they must always be borne in mind when inter-

preting results. With these reservations a negative reaction with intradermal tuberculin is usually of valuable help in excluding tuberculosis.

(*b*) A positive intradermal tuberculin reaction at the most means that the patient has at some time or other been infected with tuberculosis: one of the present cases throws some doubt even on this conclusion. If the test is not carefully controlled it may not even mean this, and the older the child the more likely is the tuberculin test to be useless in the diagnosis of the nature of the illness affecting individual patients. But where this age limit is to be fixed, below which a positive test is to be accepted as of value, is most difficult, and in the present series even at fifteen months of age one child gave a positive tuberculin reaction while recovering completely from a streptococcal empyema. According to figures produced by Mantoux and Lemaire (17) in 1909, approximately 50 per cent. of 'healthy' children in Paris between two and four years of age gave a positive reaction to tuberculin intradermally, and even modern figures for London children (Schlesinger and Hart) (18) in 1930, indicate that among hospital out-patients, not in contact with tuberculosis in the home, one-fifth are positive to tuberculin intradermally by six years of age. Even in the early years of life, therefore, there is a very wide margin of error if a positive tuberculin test is to be regarded as indicating the nature of a particular patient's illness.

The positive Mantoux reaction must, therefore, be utilized for diagnostic purposes with considerable restraint. A positive result at even an early age should never be allowed to establish a diagnosis, but should merely take its place as a piece of evidence to be taken into consideration in the process of making a diagnosis, to be disregarded if necessary. After the first few years of life it becomes even more important to avoid establishing for any pathological condition in a child a diagnosis based mainly or entirely upon a tuberculin reaction. For surveys of large groups of children this test has proved its value, but for the individual patient with vague symptoms the Mantoux reaction, in common with all tuberculin tests, may be a good servant but is a dangerous master.

I am very greatly indebted to all the physicians of the Hospital for Sick Children, Great Ormond Street, for permission to publish records of cases under their care.

APPENDIX. *Details of 'Control' Group of Patients.*

Human tuberculin in standard dose of 0·1 c.c. used in each case.

Initials.	Sex.	Age. yrs.	Age. mos.	Final Diagnosis.	Results with Tuberculin. 0·01 mg.	0·1 mg.	1 mg.	Control Result.	Remarks.
P. H.	M	4 weeks		Pyloric stenosis	—	neg.	—	—	
J. K.	M	5 weeks		Pyloric stenosis	—	neg.	—	—	
A. C.	M	5 weeks		Gastro-enteritis	—	neg.	—	neg.	
L. S.	M	8 weeks		Pyloric stenosis	—	neg.	—	—	
J. R.	M	—	6	Absent abdominal muscles	—	neg.	—	—	
J. J.	F	—	6	Gastro-enteritis	—	neg.	—	—	
E. T.	M	—	6	Pyelitis	—	neg.	—	—	
J. W.	F	—	6	Septicaemia	—	neg.	—	—	
F. W.	M	—	6	Gastro-enteritis	—	neg.	—	—	
J. F.	F	—	8	Gastro-enteritis	—	neg.	—	—	
V. W.	M	—	8	Gastro-enteritis	—	neg.	—	—	
L. C.	M	—	10	Cirrhosis of liver	—	neg.	—	—	
J. M.	F	1	—	Rickets	—	neg.	neg.	—	Neg. to 0·2 mg.
E. K.	F	1	2	Otitis media	neg.	neg.	neg.	—	
E. J.	F	1	2	Poliomyelitis	—	neg.	—	—	
M. W.	F	1	2	Habit spasm	—	neg.	—	—	
P. L.	M	1	3	Rickets	—	neg.	—	—	
W. R.	M	1	3	Hydrocephalus	—	neg.	—	—	
H. K.	F	1	3	Cerebral diplegia	—	neg.	—	—	
S. S.	M	1	8	Mental deficiency	—	neg.	neg.	—	
J. N.	M	2	3	Mental deficiency	—	neg.	—	—	
E. F.	F	3	6	Pyelitis	—	neg.	—	neg.	
H. N.	M	3	10	Epilepsy	—	neg.	—	—	
D. H.	F	4	11	Chorea	—	neg.	—	—	
H. L.	F	5	—	Indigestion	—	neg.	—	—	
M. W.	F	5	—	Pyelitis	—	neg.	—	—	
C. C.	F	5	3	Chorea	—	neg.	—	—	
J. F.	F	5	3	Nephritis	—	neg.	—	—	
R. S.	M	5	6	Tape-worm	—	neg.	—	pos.	Neg. to 0·2 mg.
F. B.	M	5	6	Chorea	—	neg.	—	—	
D. G.	M	5	6	Empyema	—	neg.	—	—	
A. F.	F	5	11	Rheumatic carditis	—	neg.	—	neg.	
T. H.	F	6	4	Chorea	—	neg.	—	—	
I. W.	F	6	9	Tonsillitis	—	neg.	—	—	
E. D.	F	7	—	Congenital syphilis	—	neg.	—	—	
R. F.	M	7	—	Purpura	—	neg.	—	—	
I. L.	F	7	—	Vulvo-vaginitis	—	neg.	—	—	
I. W.	F	7	—	Chorea	—	neg.	—	—	
D. E.	F	7	5	Rheumatic carditis	—	neg.	—	—	
J. W.	F	7	6	Rheumatic fever	—	neg.	—	—	
P. O.	F	7	6	Pyelitis	—	neg.	—	—	
R. W.	F	7	6	Chorea	—	neg.	—	—	
F. M.	F	7	6	Rheumatic carditis	—	neg.	—	—	
K. H.	F	7	9	Diabetes	—	neg.	—	—	
V. P.	F	7	9	Nephritis	—	pos.	—	pos.	
B. C.	F	7	10	Jaundice	—	neg.	—	—	
C. T.	M	8	—	Rheumatic carditis	—	neg.	—	neg.	
R. H.	M	8	—	Rheumatic fever	—	pos.	—	pos.	
R. W.	M	8	—	Tonsillitis	—	neg.	—	—	

APPENDIX (*continued*).

Initials.	Sex.	Age. yrs.	Age. mos.	Final Diagnosis.	Results with Tuberculin. 0·01 mg.	0·1 mg.	1 mg.	Control Result.	Remarks.
J. S.	M	8	—	Rheumatic carditis	—	neg.	—	—	
B. B.	M	8	—	Purpura	—	pos.	—	pos.	
F. F.	F	8	—	Polio-encephalitis	—	neg.	—	—	
C. G.	M	8	—	Diabetes	—	neg.	—	—	
E. B.	F	8	—	Rheumatic carditis	—	neg.	—	—	
N. E.	M	8	3	Chorea	—	neg.	—	—	
I. C.	F	8	6	Chorea	—	neg.	—	neg.	
G. F.	M	8	6	Rheumatic carditis	—	neg.	—	neg.	
S. W.	M	8	6	Rheumatic carditis	—	pos.	—	pos.	
E. H.	M	9	—	Rheumatic carditis	—	neg.	—	—	
E. S.	F	9	—	Rheumatic carditis	—	neg.	—	—	
A. P.	M	9	—	Rheumatic carditis	—	neg.	—	—	Test done twice
D. G.	F	9	—	Rheumatic carditis	—	pos.	—	pos.	
J. P.	F	9	2	Rheumatic carditis	—	pos.	—	pos.	
I. S.	F	9	5	Chorea	—	neg.	—	—	
E. K.	F	9	6	Chorea	neg.	neg.	neg.	—	
R. S.	M	9	6	Rheumatic carditis	—	neg.	—	—	
J. H.	M	9	6	Rheumatic carditis	—	neg.	—	neg.	
A. P.	M	9	6	Cirrhosis of liver	—	neg.	—	neg.	
M. F.	F	9	11	Constipation	neg.	pos.	—	—	Curious result
V. T.	M	10	—	Rheumatic carditis	—	neg.	—	—	
C. B.	F	10	—	Chorea	—	neg.	—	—	
M. H.	F	10	—	Chorea	—	neg.	—	—	
J. K.	F	10	—	Rheumatic carditis	—	neg.	—	—	
I. C.	F	10	—	Rheumatic carditis	—	neg.	—	neg.	
M. T.	F	10	6	Rheumatic carditis	—	neg.	—	neg.	
E. O.	F	10	6	Pyelitis	—	neg.	—	neg.	
L. C.	F	10	6	Cerebral diplegia	—	neg.	—	—	
E. B.	F	10	6	Rheumatoid arthritis	—	neg.	—	—	
L. H.	F	11	—	Tonsillitis	—	neg.	neg.	—	
M. L.	F	11	—	Rheumatic fever	—	neg.	—	—	
H. M.	M	11	—	Nephritis	—	neg.	pos.	—	Curious result
D. L.	F	11	—	Pericarditis	pos.	pos.	—	—	?Tuberculosis
V. W.	F	11	—	Chorea	—	neg.	—	—	
F. A.	F	11	—	Rheumatic carditis	—	pos.	—	pos.	
V. D.	F	11	—	Cardiospasm	—	pos.	—	pos.	
E. H.	F	11	—	Rheumatic carditis	—	neg.	—	—	
V. B.	F	12	—	Cardiospasm	—	pos.	—	—	
R. H.	F	12	—	Diabetes	—	neg.	—	—	

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INTESTINAL CARBOHYDRATE DYSPEPSIA[1]

By ARTHUR F. HURST and F. A. KNOTT.

With Plates 7 and 8.

Intestinal carbohydrate dyspepsia is one of the commonest abdominal disorders, although in the majority of English books on medicine it is not even mentioned. The following account is based on a study of a large number of cases, twenty-four of which have been investigated in great detail at New Lodge Clinic.

Starch Digestion in Man.

Under normal conditions the starch taken in food is digested by the ptyalin of the saliva, the amylopsin of the pancreatic juice, and the diastase of the juice secreted by the small and large intestines. The ptyalin is least important, as it is destroyed by the first trace of free hydrochloric acid with which it comes in contact in the stomach; consequently salivary digestion of starch only continues in the stomach for any length of time in the centre of lumps of insufficiently chewed food. The amylopsin, which has up to now been held to be solely responsible for the initial break-down of starch in the small intestines, is certainly not the only or even the most important diastatic ferment present. This is proved by the fact that the digestion of starch was unimpaired in all the cases of pancreatic disease we have investigated, though much undigested fat and protein were found in the stools. We have also been able to demonstrate the presence of a diastatic ferment in specimens of the duodenal contents obtained through a Ryle's tube in cases of complete obstructive jaundice in which bile and trypsin were absent and in which a normal quantity of free acid was secreted by the stomach. It is clear, therefore, that the intestinal juice contains an active diastatic ferment. This diastase appears to be essential for the efficient digestion of starch: when for any reason its secretion is deficient, a more or less considerable quantity of unaltered starch reaches the colon. It has hitherto been taught by physiologists that the succus entericus contains no starch-splitting ferment, and there is in fact no direct evidence to the contrary, except for some observations carried out on a single case by Esser in 1908. A patient with polyposis of the colon had a caecostomy performed. After a time a number of polypi projected out of the stoma and the clear, pale

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yellow juice secreted by their mucous membrane, which was found on microscopical examination to be similar to that of the healthy colon, was collected; it was found to contain a powerful amylolytic ferment.

It was formerly believed that the starch in vegetable food could be digested only when the cellulose envelopes had been broken open by cooking, or, if eaten raw, after it had been dissolved by the action of a hypothetical cellulose-splitting ferment in the small intestine (Adolf Schmidt) or of bacteria in the colon. Strasburger has, however, recently shown that the cellulose walls of vegetable cells are not broken by cooking. Moreover, a cellulose-splitting ferment has never been proved to exist in the human alimentary tract, and it is now known that bacteria do not normally take any part in the digestion of carbohydrates, which in healthy individuals is almost confined to the jejunum. We have confirmed the majority of Strasburger's observations. In all ordinary cooked starchy food most of the grains are swollen but not burst open, a condition illustrated in Pl. 7, Figs. 1 and 2, which represent respectively the raw starch grains of a potato stained with iodine and the same grains after exposure to water at only 60° C. for thirty minutes. The increase in size is very great, but the large majority of the envelopes, though distended, are not broken.

The distribution of bacteria in different parts of the intestines is of great importance for the normal digestion of carbohydrates.

Some work on this subject was reviewed by one of us (F. A. K.) in the Guy's Hospital Reports in 1927, and at the same time he recorded the results of systematic duodenal and jejunal incubation. His findings have since been confirmed and amplified by Arnold and Brody in America in experiments on men and dogs. When the stomach is secreting a normal amount of hydrochloric acid and the patient is taking an ordinary mixed diet, the average reaction (pH) at the different intestinal levels is found to differ considerably from those at one time assumed to exist. According to whether material from the stomach is actually entering the small intestines or the resting stage exists, the reactions at the different levels vary thus: duodenum pH 5·6–6·0, jejunum (upper half) pH 5·5–6·5, jejunum (lower half) 6·0–7·0, and ileum 6·8–8·0. Not until the ileum is reached does the average reaction represent that at which most of the intestinal bacteria can multiply freely, viz. pH 7·4. At a higher level the acidity is such that only organisms resistant to an acid medium will flourish. It is thus apparent why in normal people no bacteria beyond a few Gram-positive cocci are found in the duodenum and upper jejunum and why only the lower jejunum has a permanent flora, which consists mainly of organisms of the aciduric type. The faecal type of flora (coliform bacilli, anaerobes, &c.) does not normally develop above the lower ileum and caecum. We may safely assume that this tendency to auto-sterilization of the upper small intestine exists in all normal people. The gastric contents enter the duodenum not only saturated to their full buffer capacity, but usually with an excess of free hydrochloric acid, and though the free acid is rapidly neutralized by the bile and pancreatic juice, the organically combined acid is less quickly neutralized, and, with slight variations

according to the digestive phase, maintains the reaction within the duodenum and jejunum upon the acid side of that suitable for any vigorous bacterial growth. It is clear that in normal people the digestion of starch and the absorption of the products of its digestion occur in the almost complete absence of bacteria. We have seen that when carbohydrate food prepared in the ordinary way is eaten, some of it reaches the small intestine as starch completely freed from its envelopes and some as the large, swollen but unruptured grains, illustrated in Pl. 7, Fig. 2. We know that the free starch is very rapidly broken down by the amylolytic ferments present, but the fate of the swollen, unruptured grains must be considered in some detail. Strasburger has demonstrated that ferments can penetrate the unbroken walls of vegetable cells and digest and extract the starch within them. We have carried out experiments on similar lines with the common varieties of starchy foods, and although during test-tube experiments no penetration of absolutely raw starch grains by pancreatic or intestinal ferments could be observed, definitely positive results were obtained when tests were applied to grains which had swollen to only a very small extent and had certainly not burst. For example, Pl. 7, Fig. 3 represents the same grains as in Pl. 7, Fig. 2 stained with iodine after ten minutes contact with fresh normal human duodenal contents. The extraction of the peripheral starch is clearly shown by the greater transparency at the edge of the grains. Some of the small grains have lost nearly all their starch. In these test-tube experiments the soluble products of the digestion of starch pass out into the surrounding media. In the living subject, owing to the absence of bacteria from the upper part of the small intestine, the starch in these swollen grains as well as the starch from the burst grains can thus be hydrolysed to sugars and absorbed without undergoing any fermentation.

Strasburger further discovered that the penetration of unbroken grains is made more easy when the protein and fat in the covering of the starch grains are digested by pepsin or trypsin and by steapsin respectively. We have confirmed this in the case of swollen grains, but not with absolutely raw starch. The acid of the gastric juice and the alkaline intestinal fluids separate the cells from each other, but they have no action on the cellulose. It is the combined action of the digestive ferments themselves which results in the extraction of starch from the unburst grains.

Pathogenesis of Intestinal Carbohydrate Dyspepsia.

We have seen that normally starch is completely extracted from its envelopes and digested in the upper part of the small intestine and none reaches the caecum. When the secretion of the small intestine is deficient, ptyalin, and especially amylopsin, can completely digest free starch or starch in cells with broken walls, but the rate of extraction and digestion of the starch in intact cells is too slow for it to be complete before the caecum is reached. Here the diastase of the caecal secretion penetrates the cells, but the dextrins

and sugars which pass from the grains into the surrounding media are attacked by saccharolytic bacteria which are present in very large numbers, and they undergo fermentation with gas production before there is time for much absorption to take place.

The symptoms of carbohydrate intestinal dyspepsia are caused by the carbon dioxide and acetic, butyric, and other organic acids produced by this fermentation in the caecum and ascending colon.

This effect of infected surroundings on starch digestion can be clearly demonstrated by a simple experiment. If a suspension of ordinary uncooked starch, such as that from potatoes, in normal saline solution is inoculated with a loopful of mixed faecal bacteria obtained either from a normal individual or from a patient with carbohydrate intestinal dyspepsia and is then incubated overnight, surprisingly little bacterial growth takes place and little or no gas is produced. If, on the other hand, the experiment is repeated, but a small amount of active diastase or fresh duodenal contents is added, a great increase in bacterial growth and gas production occurs. Similarly, if two tubes are filled, as in Pl. 7, Fig. 4, one with pancreatic extract and starch alone and the other with pancreatic extract, starch, and bacteria, large quantities of gas develop in the infected and practically none in the non-infected tube. The presence of active diastase continually producing sugars is evidently the determining factor in the fermentative process.

Further, when a simple filtrate of a faecal emulsion obtained from a patient with intestinal carbohydrate indigestion is prepared, although much undigested starch is present in the stools, the filtrate contains considerable quantities of diastatic and tryptic ferments. Thus in the large intestines of these patients resolution of the starch must continue, the sugars produced providing ample material for gas production by any coliform, micrococcal, or anaerobic bacteria present. By way of contrast it is interesting to note that in the course of these observations starch-containing stools have occasionally been found which did not ferment to any extent. Some of these stools have contained simply a few small, undoubtedly quite raw starch grains or similar grains with raw plant structures, which, as explained above, are probably unaffected by any digestive ferments. In fact, an exactly similar stool can be procured in any normal individual by giving a piece of raw new potato to eat. For fermentation to occur the undigested grains must be in a swollen, though not necessarily ruptured condition (vide Pl. 8, Figs. 5, 6, and 7). On the other hand, in the filtrates from a few non-fermentative specimens either the diastase was extremely low or the acidity of the specimen was high and bacterial growth suppressed. The explanation of this last condition is given later. In these cases ferments may or may not have been deficient in the colon as well as the small intestine, but the important point is that, in the absence of active diastatic resolution of the starch, obvious and excessive fermentation did not occur.

In seven out of a series of twenty-four cases there was direct microscopic

evidence of catarrh, as excess of mucus and epithelial debris was found intimately mixed in the faeces. Although in no case was there any evidence of existing infection of the intestines or gall-bladder, and blood, whether obvious or occult, and pus cells were never present in the stools, yet thirteen of the patients had in the past suffered from one or more attacks of dysentery, typhoid fever, or food poisoning, four gave a history of acute jaundice and four had been operated upon in the past for acute appendicitis. All dated their symptoms from these attacks. Only four failed to give a history of past infection of the intestinal canal. Adolf Schmidt found slight inflammation confined to the upper part of the small intestine in a patient with typical carbohydrate intestinal dyspepsia who had died of an intercurrent disease.

The condition can only develop if the damage is confined to the small intestine and the stomach and colon are spared. Thus it is never associated with achlorhydria, as the ptyalin of the saliva can compensate for the absence of the small intestine diastase when there is no free acid in the stomach to destroy it. We found by actual experiment that ptyalin can penetrate slightly swollen starch granules, and it is certainly as efficient a diastatic ferment as any artificial preparation. Of our 24 cases 11 had a normal curve of acidity, 13 had high normal curves or hyperchlorhydria, and only 1 had hypochlorhydria. When colitis is present as well as enteritis, the undigested starch which reaches the caecum passes rapidly through the whole colon without undergoing digestion, as the digestive secretion of the colon is as deficient as that of the small intestine and little or no diastase is present in the faeces. Consequently no sugar is set free and no fermentation occurs either in the colon or on incubation of the stools, in spite of the fact that they may contain a considerable quantity of starch. In ordinary cases of colitis, however, the small intestine is unaffected, so that the digestion of starch is perfect and the stools contain no excess of starch even if there is severe diarrhoea. In none of our cases of carbohydrate dyspepsia was there any evidence of general insufficiency of pancreatic ferments, as the fat was always perfectly digested, and in only two was there any appreciable amount of undigested muscle fibres.

Symptoms.

The chief symptom of intestinal carbohydrate dyspepsia is a widespread feeling of discomfort and fulness in the lower part of the abdomen caused by distension of the colon with carbon dioxide. In no case was this associated with excessive indulgence in starchy food. In one third of our cases the patients actually volunteered the fact that starchy food upset them and was therefore deliberately avoided. It is often most marked just after meals as a result of exaggeration of the gastro-colic reflex, the existence of which was demonstrated by Hurst and Alan Newton in 1913, and before defaecation. The discomfort is often greatest during the night and is a very common cause of insomnia. One patient of ours woke regularly at 4 a m. owing to the noise in his intestines;

he had no discomfort, but the noise often kept him awake for an hour or more. His nights ceased to be disturbed as soon as the excessive fermentation was prevented. Chemical stimulation by the carbon dioxide and organic acids together with distension by the gas may cause spasm; the patient then complains of actual pain, this condition being, we believe, the commonest cause of colon spasm. Excessive quantities of odourless flatus are passed, and some relief is always felt after its escape. Constipation occurs only if the condition is associated with spasm, and it may then alternate with diarrhoea caused by continuous irritation of the mucous membrane by the carbon dioxide and organic acids. More frequently the bowels are regular and the stools are formed, but there is always a tendency to attacks of mild diarrhoea with the passage of two to six thin, but not fluid, bright yellow stools, which have an unpleasant sour, but not putrefactive odour. The diarrhoeic stools always contain an obvious excess of undigested vegetable matter, and if kept for some hours bubbles appear as a result of fermentation of the undigested carbohydrates they contain.

We have sigmoidoscoped a number of cases in which severe diarrhoea was present. The mucous membrane of the bowel has always looked perfectly normal, but the nature of the condition can at once be recognized, as the soft faeces are seen to contain innumerable minute bubbles of gas. The long continued diarrhoea may give rise to haemorrhoids, and we have seen two cases which had been treated for months as ulcerative colitis on account of the presence of haemorrhoidal blood in the liquid stools.

Although the fermentation in the intestines is presumably continuous, it is a remarkable fact that patients with carbohydrate intestinal dyspepsia feel much more desire to pass wind during the night and when their bowels are first opened in the morning than during the rest of the day. This is probably a result of posture. During the day the gas accumulates especially in the splenic flexure, which is the highest part of the colon. To a less extent it accumulates in the shorter and less angular hepatic flexure and in the proximal part of the pelvic colon which then rises out of the pelvis. At night the whole colon is on approximately the same plane, so that the gas easily travels to the rectum. Some patients discover that they get relief at night by lying in a semiprone position, which raises the rectum above the level of the rest of the intestine, so that the gas soon collects in the rectum from which it is easily evacuated.

The accumulation of gas in the splenic flexure in the erect position often gives rise to local discomfort, which the patient mistakenly thinks is due to gas in the stomach. In his efforts to get rid of it he often swallows air, but the evacuation of this from the stomach naturally gives no relief.

The stools should be examined whilst the patient is on his usual diet; the special test-diet advocated by Adolf Schmidt is quite unnecessary. Microscopical examination reveals the presence of large numbers of starch granules which are stained blue-black with iodine. Few or none are present in normal faeces.

The undigested starch in the faeces is still within its cellulose envelope.

A group of faecal starch grains from a typical case is shown in Pl. 8, Fig. 5; a little 10 per cent. iodine in alcohol has been mixed with the specimen. No starch has been extracted. The black stain extends uniformly through the grain. Pl. 8, Figs. 6 and 7, photographed from preparations made in exactly the same way, illustrate the gradual extraction of the starch from within the cellulose envelope, which itself apparently remains intact. Pl. 8, Fig. 8 shows a cellulose envelope, from which all the starch has been removed—a common sight in any normal faeces. In contrast with the stools in pancreatic achylia, there is no excess of fat or of striated muscle fibres.

The bacteriology of these stools is important, as definite variations from the normal occur, which have in the past often been regarded as primary and therefore pathological. It can, however, be easily proved that they are simply the result of the fermentation. In the first place an excess of fermentable sugar is present in the intestinal contents; this acts as an excellent medium for the enterococci, the number of which is therefore greatly increased. Then, as fermentation continues and the faeces traverse the colon, the faecal acidity gradually rises and may sometimes even pass beyond the reaction most suitable for the common predominant bacteria. On giving a starch-free diet the excess of enterococci rapidly disappears. It is clear, therefore, that the bacterial variations are not the cause of the condition, as has generally been supposed, but the result of the excess of starch and sugar present in the colon. By the time the stool is passed in patients with intestinal carbohydrate dyspepsia, it is either already very acid or very quickly becomes so. This is the reason why Cannon, when testing the stools for viable organisms, found that bacteria tolerant of acid, e.g., bacilli of the aciduric group (*B. acidophilus, B. bifidus*, &c.) and the coarser micrococci tended to increase at the expense of coliform and other common faecal strains. It also accounts for the 'excess of streptococci' usually found in simple aerobic plate cultures made on the usual media, because such plates record, not the absolute, but only the relative number of organisms. When there is much delay in the passage of the stool owing to constipation, this acidity may be so marked that only organisms of the aciduric group remain. Thus repeated cultures on ordinary plates of three of the stools examined in this series of cases gave the remarkable result of remaining absolutely sterile. The acidity of the faecal specimens had risen to pH 4 and the faecal flora were almost entirely aciduric in type.

By examining the stools in intestinal carbohydrate dyspepsia at different times, during looseness and constipation or after laxatives, and by comparing the results or allowing the fermentative changes to continue artificially outside the body, it became clear that, as in artificial cultures, the production of acid tends to make the bacterial growth, and with it the gas production, self-limiting. For these reasons, as the acidity rises, both bacterial growth and diastatic activity cease. In assessing the laboratory findings on a faecal specimen as correctly representing the conditions actually present in the large intestine, one must be sure that it is fresh and that there is no constipation.

The fermentation test devised by Adolf Schmidt, who with Strasburger, in 1901, was the first to recognize this condition, to which he gave the name of *Gärungsdyspepsie*, gives a striking demonstration of its nature, though the microscopical examination of the stools is sufficient to make the diagnosis certain. A small quantity of faeces is mixed with water and incubated for twenty-four hours, any gas given off being collected. No gas is evolved from normal stools. In intestinal fermentative dyspepsia (Pl. 8, Fig. 9), the fermentation which has been taking place in the colon continues *in vitro*, and a considerable quantity of odourless gas is evolved, the faeces at the same time becoming very acid. In putrefactive diarrhoea, which is due to insufficient digestion of meat, a smaller quantity of foul gas is evolved, and the faeces become strongly alkaline.

Treatment.

The treatment of carbohydrate intestinal dyspepsia is very simple. Sugars are perfectly digested, and in all but the most severe cases in which chronic diarrhoea is present, free starch, as in flour and bread, is well digested, as the pancreatic amylopsin can very easily deal with this. As there is very little starch in green vegetables it is also unnecessary to prohibit them, unless irritation of the intestines by the products of fermentation has been sufficiently great to make it necessary for a time to avoid anything which irritates the mucous membrane mechanically. In severe cases, therefore, it is best to exclude vegetables of every kind and also rice. In milder cases, and in more severe ones as soon as the diarrhoea has ceased, green vegetables can be allowed as purées, and at a still later stage there need be no limitation in anything but root vegetables, cauliflower, and rice. In most cases after a comparatively short time it is possible to make the restrictions gradually less severe until finally nothing but potatoes are prohibited. Occasionally after a time the power of digesting starch returns completely, but more commonly potatoes have to be avoided or greatly restricted for the rest of the patient's life, and in severer cases the permanent restriction extends to all root vegetables and rice.

Progressive changes in the diet can be most satisfactorily controlled by examining the stools, which should at no time contain any excess of starch or produce any gas on incubation. The excess of enterococci should also disappear within a few days of commencement of treatment and should at no time reappear. In milder cases, however, the patient's symptoms are a sufficient guide to treatment, as so long as he feels comfortable and passes no excess of gas, the restrictions in diet can be presumed to be sufficient.

We have generally given an active preparation of an amylolytic ferment with each meal, as when this is done it appears that less restriction in diet is necessary. We have found that vegetable diastases are more resistant to passage through the gastric acid than the amylopsin of pancreatic extracts, which is rapidly destroyed by the gastric juice. Moreover, the main ferment of pancreatic extracts is tryptic, not diastatic, so that bulk for bulk there is more diastase in vegetable

preparations than in pancreatic extracts. The use of a vegetable diastase should be continued for a considerable period, especially if an attempt is made to give potatoes again.

Formerly we also gave a tablespoonful of powdered charcoal in a small quantity of water morning and evening to absorb any gas which was still produced. This is, however, quite unnecessary if a sufficiently strict diet is ordered. It is much better to prevent the production of gas than to provide for its absorption, as the condition can be permanently cured only by curing the enteritis, which is kept active by the mechanical irritation of undigested vegetable matter and the chemical irritation of the production of bacterial activity on starch.

In severe cases with much diarrhoea the administration of a teaspoonful of chalk three times a day hastens recovery, as the irritating organic acids are then neutralized as soon as they develop (Porges and Essen).

As the excess of enterococci present is a result and not the cause of the condition, which is due to deficiency of succus entericus and not an infection with streptococci or other organisms, vaccine treatment is quite useless. We have seen many patients rapidly cured by diet alone after having undergone many months of treatment by inoculation without the slightest benefit. Colonic lavage, which is almost as popular a treatment, is of course equally futile.

The recognition of the true nature of the condition and its rational treatment is of the greatest importance for many neurasthenic and psychasthenic individuals, whose condition is much aggravated by the insomnia caused by carbohydrate intestinal dyspepsia, with which it is often associated. We have often found in such cases that a suitable diet alone rapidly cures long-standing insomnia, which has failed to respond to treatment by drugs, such as medinal and luminol.

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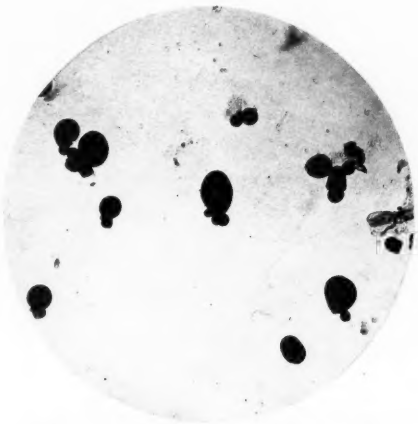

FIG. 1. Raw potato starch stained with 10% iodine in alcohol. × 70

FIG. 2. Same starch grains as in Fig. 1 after heating in water-bath at 60° C. for 30 minutes. × 70

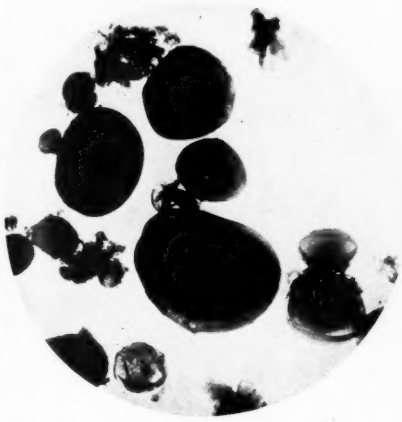

FIG. 3. Same starch grains as in Fig. 2, but after 10 minutes exposure to fresh duodenal contents

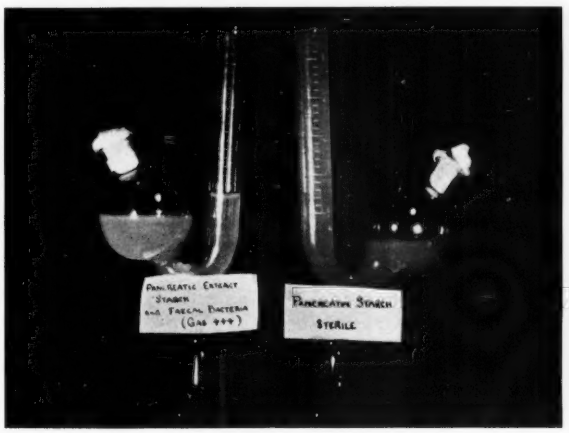

FIG. 4. Experiment showing influence of bacteria and diastase in gas production

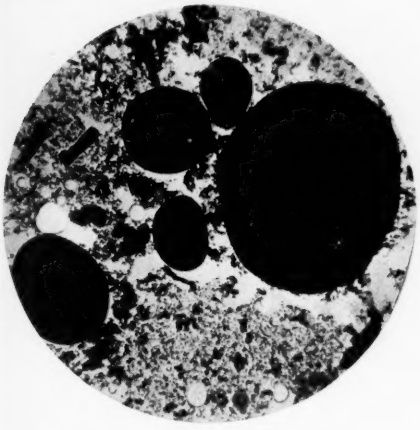

FIG. 5. × 70

FIG. 6. × 70

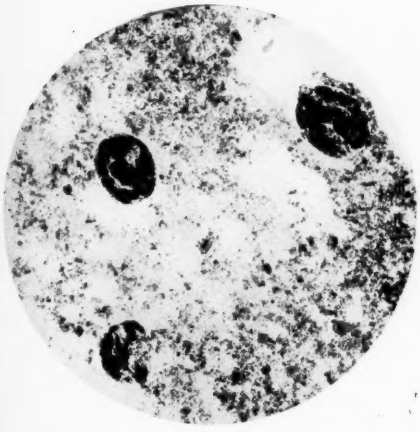

FIG. 7. × 70

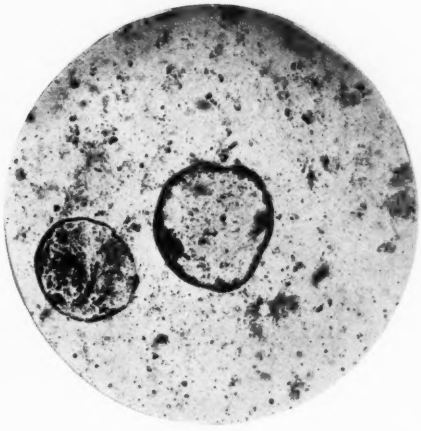

FIG. 8. × 70

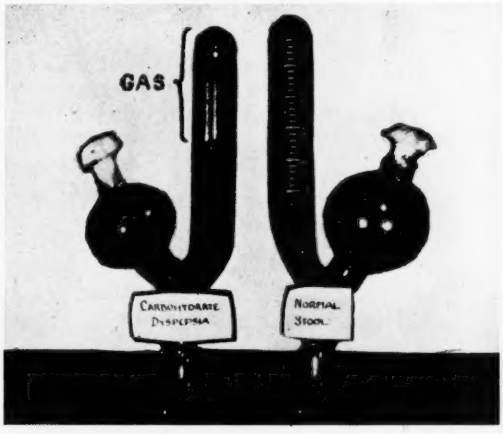

FIG. 9. Carbohydrate dyspepsia (left) compared with normal (right). Faecal fermentation tests applied to similar amounts of faeces. The left hand tube contains much gas, the right hand tube practically none.

616.24.8

THE HYPOCHLORHYDRIA OF ASTHMA IN CHILDHOOD[1]

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I. *Introduction.*

From the earliest times 'digestive upsets' have been noted by all observers in association with the asthmatic habitude, and dietetics has proved one of the main strongholds of the therapeutist. Floyer, in his *Treatise of the Asthma*, published in 1698, and incidentally the first book in English dealing exclusively with the subject, states:

'Some writers, as Sylvius and Etmuller, have observed the hypochondriac symptoms in the stomach, and conclude the asthma is a hypochondriacal flatus, and wants digestives. . . . It is commonly observed that fulness of diet, and all debauches render the fits most severe, and a temperate diet makes the fits more easy. . . . This defect of digestion and mucilaginous slime in the stomach are very obvious and observed by writers, and were supposed the immediate cause of the asthma.'

Since Floyer's day most succeeding writers have assigned to the stomach and digestion an equally important aetiologic rôle. To Withers (1786) this association did not appear any anomaly, for he writes:

'As the stomach is one of the most irritable organs of the whole system . . . it cannot be in the least surprising that whatever disorders the stomach should in some measure disorder the whole system, and be so often observed to induce the asthmatic fit.'

Pridham (1860) endeavoured to probe the question a little further, and suggests that:

'It appears to me probable that the original cause of the disease was in the overworked powers of digestion. Was it not then probable that impurities in the blood were then formed by imperfect digestion which were then thrown off by means of the lungs?'

Salter (1868), the author of that monograph on asthma renowned for its accurate, clear, and detailed exposition of all phases of the subject, writes:

'At other times the precursory symptoms are connected with the stomach, and consist of loss of appetite, flatulence, costiveness and certain peculiar uneasy sensations in the epigastrium; but here I think we have something more than mere premonitory signs; I think the relation of these symptoms to the spasm which follows is often that of cause and effect.'

[1] Received October 21, 1930.

He then explains that the intimacy of this relationship that exists between the stomach and the lungs is shown in asthmatics in various ways, for (*a*) asthmatics are generally dyspeptics; (*b*) frequently attacks of asthma may be traced to errors of diet—a debauch, a late dinner, a heavy supper; (*c*) tightness of breathing follows every meal in some persons with asthmatic habitude; (*d*) starvation has a pronounced effect on the attack; (*e*) gastric symptoms are so often premonitory of an attack—flatulence, hiccough, epigastric distress, anorexia; (*f*) of all forms of prophylactic treatment none, with the exception of a change of residence, is more successful than that which is regimenal.

It is remarkable, in the face of these oft-quoted and well-established facts, that no definite endeavour has been made to determine any causal factor for such a reputed relationship. It has long been recognized that certain articles of diet disagree with certain asthmatics, but most sufferers evidence some manifestations of alimentary dysfunction as vomiting, flatulence, 'liverish turns', constipation, or bouts of mucous diarrhoea; and especially is this true of children. It is in these cases that one is astonished at the frequency with which such digestive upsets usher in the asthmatic attack, as well as at the rapidity with which it follows the ingestion of the causative food. Many cases come to one's mind where blistering of the lips and mouth and an intense urticarial eruption have occurred immediately on eating such foods as eggs or fish. Obviously, in these cases, there must be some short cut from the digestive tract to the blood stream without the aid of the numerous enzymes and digestives that one associates with the physiology of the alimentary canal.

This fact brings to mind the pioneer work of Schloss and Worthen, who, in 1916, furnished evidence that the gastro-enteric canal of normal infants is permeable to undigested protein in small amounts. Recently this phase has been advanced to a great degree by Walzer and his collaborators, especially with their work regarding the Prausnitz-Kustner reaction. Further, Donnally has shown that foreign proteins can be eliminated in the breast milk, and thus explains how infants may be sensitized to foods with which, to all appearances, they have never come in contact. Ratner has collected fifteen instances in which it appears that the mother's over indulgence in particular foods during gestation was a causal factor in the subsequent food allergy of the offspring.

Hand in hand with these clinical observations, Walker, Wetmore, and Adkinson have produced experimental evidence that when whole proteins give a strong skin or constitutional reaction the amino-acid of the corresponding protein does not. In other words, the further one gets from the true protein the less the reaction; so one infers that these 'reaction-producing substances' are destroyed by digestive processes.

Facts such as these, gleaned from both clinical and experimental observations and pointing to the undigested protein or its early cleavage products as responsible for allergic reactions, led the author to investigate the digestive functions in asthmatic children. The fact of most importance that has accrued from these endeavours is that allergic children show a diminished power of

secreting acid gastric juice in response to a meal when compared with normals. Protein digestion, in consequence, must be below par, and as a result these 'reaction-producing substances' are not destroyed.

II. *Technique.*

The fractional method of gastric analysis was employed in over 200 asthmatic children, whose ages varied from six months to twelve years. In addition, a series of controls was carried out in surgical cases, medical cases prior to discharge, and presumably normal children attending the out-patient department of the hospital.

The technique adopted may be stated briefly as follows: For several days prior to the test all medicaments were stopped, and from the previous evening food was forbidden. In the morning, between eight and nine o'clock, a Ryle's stomach tube was passed and all the fasting juice drawn off, the tube remaining in position until the completion of the procedure.

Two varieties of meal were employed:

1. Oatmeal gruel (Rehfuss). This is made by boiling two tablespoonfuls of fine breakfast oatmeal in a quart of water until the bulk is reduced to a pint; the mixture is strained and sweetened; no salt was added.

2. Alcohol (Cheney). A 7 per cent. dilution of ethyl-alcohol of neutral reaction in distilled water was employed. From 20 to 40 cubic centimetres were used, depending on the size of the child. This was passed by means of a syringe directly down the tube into the child's stomach.

Each meal has its advantages and disadvantages. The advantage of the oatmeal gruel is that it affords some estimate of the emptying time of the stomach and of the activity of the salivary ferments by means of the iodine test for starch. In children its disadvantages are many—difficulty is often experienced and time wasted in getting a child to swallow a pint of tasteless gruel with the additional discomfort of a tube in the mouth; a lot of time and trouble is expended in preparing the meal, especially when several are to be done in one morning; the quantity taken necessarily dilutes any juice secreted and so lowers the readings mostly during the first hour; the result when drawn off is frequently thick and sticky.

The advantage of the alcohol meal is that most of these disadvantages are overcome. The meal can be kept in stock ready for immediate use; it is passed directly into the stomach, obviating loss of time or trouble in getting it down; no taste, smell, or psychic effect is involved; the small volume utilized does not introduce such a dilution factor as the gruel; and a clear juice is obtained. Alcohol is a good gastric stimulant. Its one disadvantage is that no index is afforded of the emptying time of the stomach or of salivary ferment action.

Each fifteen minutes after introducing the meal about ten cubic centimetres of gastric contents are drawn off through the tube by means of a syringe until

twelve specimens are obtained, the whole process taking two and three-quarter hours.

The biochemical investigations are carried out by titrating a measured volume of each specimen in turn against a decinormal soda solution. The free hydrochloric acid is determined by titration to the end-point with dimethyl; and the total acidity to the end-point with phenolphthalein. Total chlorides are estimated by the method of Claudius, somewhat modified. The figures which result are plotted on charts drawn up according to the findings of Bennett and Ryle, where the shaded area marks the average limits in 80 per cent. of normal people.

A unit of hydrochloric acid is defined as the equivalent of one cubic centimetre of decinormal hydrochloric acid for each hundred cubic centimetres of gastric contents. The classification adopted is according to the highest peak of free acid attained. The groupings may be compared with Bell's classification, and with Bennett and Ryle's curve for normal persons:

Group.	Author.	Bell.	Bennett and Ryle's Chart.
I	No free acid	Achlorhydria	Along base line
II	Under 10 units	Hypochlorhydria	Below shaded area
III	Under 20 units	Low normal	Lower limit of shaded area
IV	Under 30 units	Normal	Central zone of shaded area
V	Over 30 units	High normal	Upper limit of shaded area
VI	Over 60 units	Hyperchlorhydria	Over 60 unit line

III. *Summarized Results of 200 Fractional Gastric Analyses in Asthmatic Children.*

In 9 per cent. of the cases there was a complete absence of free hydrochloric acid over a period of 2¾ hours following the meal; in 48 per cent. there was a pronounced hypochlorhydria; and in 23 per cent. a mild hypochlorhydria. Thus, in 80 per cent., or four out of every five, asthmatic children the response of acid gastric secretion was below the average normal.

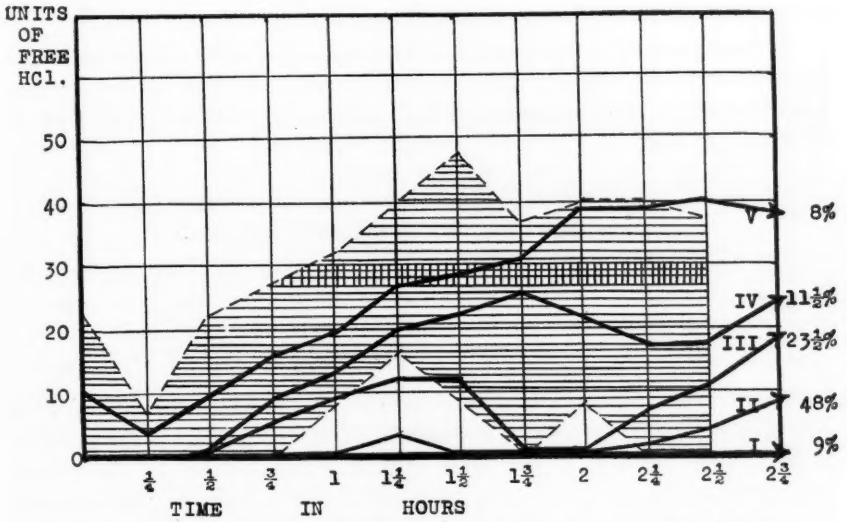
In Table I the actual results obtained are tabulated according to age, sex, and the highest point of the curve attained, expressed as units of free hydrochloric acid.

A visual conception of these results is afforded by Graph 1, where the percentages manifesting each type of acid curve are portrayed and compared with the normal limits as evidenced by the shaded area. The average reading for normal children is from 25 to 30 units. In 80 per cent. of asthmatic children this zone is never reached.

Comparison of methods. To obviate any chance of error the two methods of meal, as already outlined, were used equally and indiscriminately both for afflicted and normals. The advantages and disadvantages of each have been discussed previously. One hundred asthmatic children were submitted to each procedure, and it has been thought of interest to tabulate the results of each group separately, so that any defects or differences may be apparent.

TABLE I. *Summarized Results of 200 Fractional Gastric Analyses in Asthmatic Children Classified According to the Highest Peak of Free Hydrochloric Acid attained, as well as to Age and Sex.*

	Highest number of units of free HCl.					Sex-incidence.		
Age in Years.	None 0	Under 10.	Under 20.	Under 30.	Over 30.	Males.	Females.	Total.
1	—	2	—	—	—	1	1	2
2	—	2	—	—	—	1	1	2
3	2	6	—	2	1	9	2	11
4	3	10	2	—	—	12	3	15
5	3	16	7	4	—	24	6	30
6	2	20	11	2	1	22	14	36
7	2	16	12	2	3	25	10	35
8	1	12	4	6	5	19	9	28
9	3	7	4	3	4	16	5	21
10	1	3	3	3	1	7	4	11
11	1	2	4	1	1	6	3	9
Total	18	96	47	23	16	142	58	200
Males	14	65	31	17	15	142	—	—
Females	4	31	16	6	1	—	58	—
Per cent.	9	48	23½	11½	8	71	29	—



GRAPH 1. Summarized results of 200 fractional gastric analyses in asthmatic children.

The percentage results are expressed according to the type of curve manifesting them; the shaded area represents Bennett and Ryle's findings in 80 per cent. of normals; and the double-shaded area represents the zone reached in normal children according to most observers.

This similarity of results is most striking and impressive, and, when one considers the ease and simplicity of the alcohol meal, diverts one to favour its routine use, except in cases where it is important to know the emptying rate of the stomach.

TABLE II. *Comparison of Results According to Type of Meal Employed.*

Highest Peak.	Oatmeal.	Alcohol.	Total Per cent.
None	12	6	9
10 units	45	51	48
20 units	22	25	23½
30 units*	12	11	11½
Over 30 units	9	7	8
Total cases	100	100	—
Males	74	68	—
Females	26	32	—

In several cases the same child has been submitted to each procedure. Although the highest peaks attained have been very similar, the individual curves have shown one or two differences. With the oatmeal there is a drop or absence of acid in specimens drawn off during the first hour, and the curve tends to rise toward the end of the third hour. With the alcohol there is a gradual rise to the peak, then a fall; and one or two more specimens contain acid than with the gruel. In the border-line cases between achlorhydrics and hypochlorhydrics alcohol appears a greater stimulant than the gruel, as some evidence of acid secretion may appear in one specimen. Hence the drop in the achlorhydrics in Table II from twelve to six per cent.

In many countries the Ewald method is employed, and only one reading is taken, from three-quarters to one hour after the meal. In Table III the readings according to the fractional method over three hours are compared with those of the hour specimen.

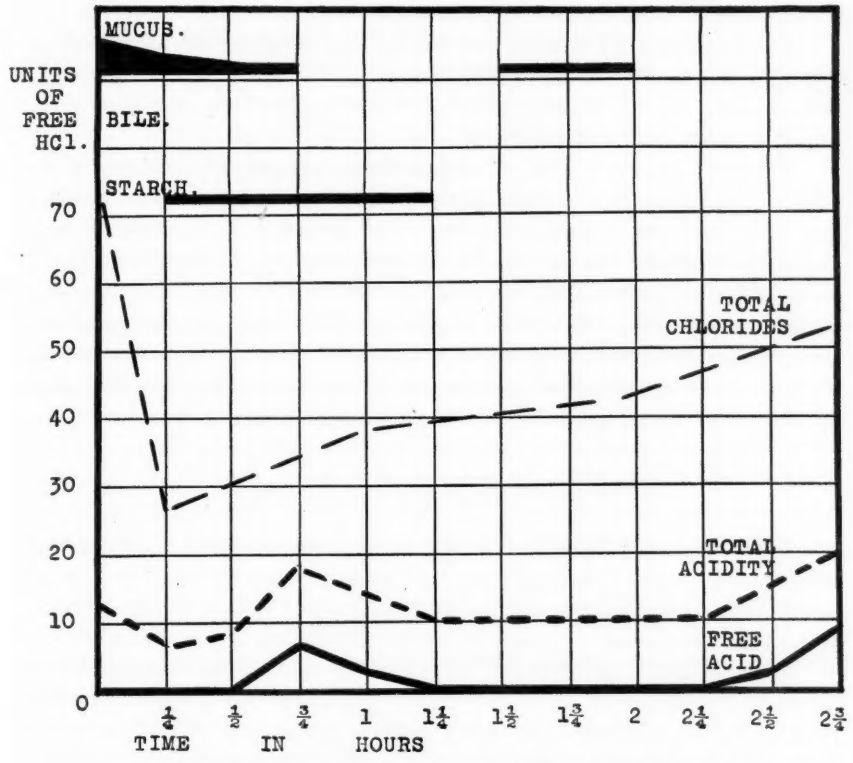
TABLE III. *Comparison of Results according to Fractional Method over Three Hours and those of the Hour Specimen.*

Highest Peak of Free Acid.	Nil.	Under 10.	Under 20.	Under 30.	Over 30 Units.
By fractional analysis	12	45	22	12	9
Hour specimen (Ewald)	48	34	14	4	—
Average number of specimens containing acid	—	4	7	9	9

These figures are tabulated from the 100 cases in which the oatmeal gruel was employed, and serve to emphasize the marked deficiency in the power of secreting acid gastric juice that occurs in these asthmatic children. The average number of specimens which contain free acid are also given, and one notes the small percentage of the twelve specimens that contain acid in the hypochlorhydric cases. This indicates the deficiency of secretion, not only in quality, but in quantity and duration as well.

IV. *Typical Gastric Analysis in an Asthmatic Child.*

In Graph 2 a typical result of an analysis is portrayed. One notes the deficiency of hydrochloric acid both in the quantity of the secretion and in the number of specimens containing free acid. The total acidity runs parallel with the free acid curve, and the total chloride curve is a low normal. In general, one notes the presence of much mucus; and the absence of traces of bile in the specimens is a striking feature. The emptying rate of the stomach



GRAPH 2. Typical fractional gastric analysis in an asthmatic child.

varies greatly, as shown by the iodine reaction in the cases where gruel was used. Some stomachs are empty in an hour, some have not emptied at the conclusion of the test (2¾ hours). In many cases the starch is dextrinized rapidly by ptyalin action, so that at the end of a quarter or half an hour only a red coloration with iodine is obtained.

Age. Deficiency of acid secretion is more frequent and more pronounced before the age of seven years (Table I). Towards puberty the curves tend to rise; one wonders whether this fact bears any relationship to the tendency to spontaneous cure that occurs during these years, especially in boys.

Sex. Sex does not appear to exert any pronounced influence on the frequency of hypochlorhydria. One interesting fact is apparent, namely, of the thirty-nine cases with acid secretion reaching over 20 units, which, as inferred from the preceding paragraph, is more frequent over the age of seven years, only seven are girls as compared with thirty-two boys. The acid curve does not appear to rise toward puberty in girls with nearly the same frequency as in boys. Possibly one may correlate this fact with the tendency of asthma to persist in girls, or other allergic manifestation to appear, as well as with the fact that it is through the mother that the tendency to manifest some allergic trait is twice as often transmitted as through the father.

Family history. The more severe grades of deficiency are associated frequently with the more intense family history of allergy. One is led to suggest that the parents so afflicted would show a similar deficiency, but this is only true in a certain percentage of cases.

Previous illnesses. In other cases showing a pronounced deficiency of free acid the asthma has followed one of the debilitating infectious diseases of early life. The chief offenders are whooping-cough and measles, especially if complicated by a broncho-pneumonia. One knows that a hypochlorhydria frequently accompanies the course of these complaints and may last for a varying period during convalescence. One might suggest that it is during this period of temporary hypochlorhydria that the patient becomes sensitized. On the other hand, the more intensely bronchitic types or severe lung damage cases, in contrast to the dry spasmodic type, tend to show the more normal curves.

V. *Observations in Other Forms of Allergy.*

1. *In children.* Children complaining of urticaria, hay-fever, migraine, or eczema have likewise been submitted to fractional gastric analysis. Though the numbers completed are small as yet, there appears to be a similar deficiency as in asthmatics, though not quite in the same frequency or the same degree.

2. *In adults.* (*a*) *Asthma.* Many of the parents of these asthmatic children were submitted to the test if they manifested any allergic symptoms. In about half of these adults there is a definite deficiency of free acid secretion. In the other half it was normal, and in no case has it been excessive. Hurst has analysed the results of 66 test meals in cases of asthma, 61 adults and 5 children. He concludes that 'hyperchlorhydric and high normal curves were obtained as frequently among asthmatics as among normal people, but that curves below normal occurred in about 20 per cent. more asthmatics, the excess being chiefly in the hypochlorhydrias and achlorhydrias'. Duke performed gastric analyses in 24 cases of allergy, because there were stomach symptoms: 12 showed complete achlorhydria, 6 a free acidity below 5 units, and 6 normal acids. Brown states that a high percentage of sensitization cases have low gastric acidities. Rowe, in 100 cases of food allergy in adults, did 30 gastric analyses: 23 were normal, 4 hypochlorhydric, 3 achylic.

Criep and McElroy, from analyses in 50 cases of allergy, give the following table:

Allergic Condition.	Number.	Achylia.	Achlor-hydria.	Hypochlor-hydria.	Normal.	Hyperchlor-hydria.
Asthma	28	2	10	12	12	—
Hay-fever	12	—	4	4	4	1
Urticaria	6	2	3	1	3	—
Atrophic rhinitis	2	—	1	—	1	—
Angioneurotic oedema	1	—	1	—	—	—
Migraine	1	—	—	—	—	1
Totals	50	4	19	17	20	2

(Unfortunately the figures do not appear to add correctly.)

(*b*) *Other forms of allergy.* The findings as tabulated above lead one to wonder if this hypochlorhydria is a constant accompaniment of all forms of allergy in adults. Schneider and Carey, in discussing achlorhydria, state that they have found it often enough in such conditions as migraine, allergic conditions, and skin diseases as to make a direct relationship rather certain. Of the three cases of achlorhydria described by Baird, Campbell, and Hern from amongst the sixty 'normal' students tested, one was a hay-fever sufferer of several years standing. Duke has described an achlorhydria or hypochlorhydria in cases of heat and cold sensitiveness, whilst Barber, Howitt, and Knott report hypochlorhydria or achlorhydria in eight out of ten cases of light sensitization of the adult type. German dermatologists, as Ayres, Urbach, and Ehrmann, have described a low gastric acidity in the majority of a series of cases of chronic eczema. Berglund and Chang state that achlorhydria as an incidental finding is very rare in Peking, only one such instance, a 28-year-old patient with urticaria, has been found amongst 284 consecutive histamine tests in four months.

From these isolated results the worth of doing a fractional gastric analysis on any case of allergy, whether child or adult, is most obvious.

VI. *Gastric Analyses in Normal Children.*

If hypochlorhydria is so common in allergic children, the query naturally arises as to its comparative incidence in presumably healthy children. The author has had the opportunity of doing about fifty fractional test meals on an additional series of children. These comprised perfectly normal children, cases in medical wards prior to discharge, and surgical cases, mostly congenital deformities. In less than 10 per cent. was any deficiency of acid secretion manifested, the peak in general reaching from 25 to 40 units of free acid, and being maintained in the greater number of specimens. The results appear to follow the higher limits of the curve as outlined by Bennett and Ryle for normal adults.

Neale, in a large series of infants and children, did not find a single instance where the alcohol meal failed to promote a flow of acid gastric juice, though in some cases the secretion apparently ceased after 30 minutes. Chievitz and Anderson tested 127 normal infants, and all showed acid secretion. Wright

tested 250 school children, aged from 6 to 15 years, by means of the Ewald meal. Of these only 4 failed to show any free acid, the observations of free acid per year varying between 25 to 30 units.

A few observers have investigated the gastric functions of children who are substandard. Wills and Paterson tested 105 infants. Ten were healthy and showed abundant secretion; 63 were under weight and showed a lower acidity than true normals, though there was no obvious gastric defect; 32 ill children (including 5 severe eczemas in which the readings were the lowest recorded) had a lowered acidity. Copeman and Gray-Hill tested 50 children, convalescent from rheumatic heart disease and surgical tubercle, and found: 10 per cent. no free acid; 10 per cent. under 10 units; 68 per cent. from 10 to 60 units; 12 per cent. over 60 units.

Allowing a generous estimate of 20 per cent. as the maximum incidence of hypochlorhydria amongst a normal population of children, the percentage of hypochlorhydrics amongst asthmatics makes a striking comparison, and must be of some special significance in the aetiology or maintenance of that state.

VII. *Significance of Findings.*

The importance and significance of these observations, as already outlined, may be discussed under the following headings.

(*a*) *Causes of achlorhydria in young children.* Faber, in discussing this subject, says there are chiefly two: (i) parenteral febrile diseases, not only during the febrile stage, but lasting into convalescence; (ii) affections of the gastro-intestinal tract, especially infectious gastritis. Parsons, debating the etiology of this condition, puts forward the following five propositions that the achlorhydria may be due to: (i) rapid emptying of the stomach; (ii) the type of test meal used; (iii) the presence of enteral or parenteral infections; (iv) false achylia, due to a masking of secretion or an 'acid-deficit'; and (v) that it is a common factor in artificially-fed infants, particularly those who are under weight or sick.

But in the asthmatic children studied, the analyses were made during the free interval—in a few cases it was possible to carry out the test during a mild attack—and the children appeared in particularly good health otherwise. They were all non-febrile, had not suffered any serious illness or exanthem of recent date, nor did they evidence any manifestation of gastro-intestinal infection. Apparently none of the usual causes outlined are operative in these children.

According to Faber the frequency of achlorhydria increases with age. This statement appears to be reversed in the case of asthmatics, for, whilst in children a low reading is present in 60 per cent. more asthmatics than normals, in adults, according to Hurst, the figure is 20 per cent. Kohiyar, in analysing a consecutive series of 1,030 fractional gastric analyses, found that 159 were achlorhydrics and 86 hypochlorhydrics. In grouping these cases according to their age-incidence in decades, it was noticed that cases were rare before the

twentieth year (no cases under 10 were examined), that there was a rapid increase to the fifth decade (41 to 50 years), followed by a progressive decline. In the higher curves males preponderated over females by 2 : 1, and females over males in the lower curves by 5 : 3.

(*b*) *What happens to the acid?* There are several possibilities that may explain the constant acid-secreting deficiency of asthmatic children:

(i) Excessive neutralization. This may be brought about by abundant salivation, duodenal regurgitation, or excessive mucus secretion. Were this so one would expect a rise in the total chloride curve, but on no occasion where the total chlorides were estimated has any excess been noted. The presence of bile in any of the specimens is an extreme rarity.

(ii) Combination with protein. Phenolphthalein, the indicator used for the estimation of total acidity, registers acid in this form. In all cases this curve was low and ran parallel with the curve of free acid.

(iii) Deficient secretion. This is probably the true explanation, and may come about in one of four ways:

Firstly, by a mechanical effect. The specimens appear to contain a fair amount of mucus. This is not to be wondered at when one considers the immediate relief afforded in many cases by the vomiting of large quantities of thick glairy mucus, the frequent mucous stools that one sees, and the abundant mucous expectoration that usually terminates the attack. Hurst has suggested that this mucus may block, in mechanical fashion, the tiny mouths of the ducts conveying the formed acid to the stomach lumen, as well as by the neutralizing effect the mucus may have on account of its slightly alkaline nature.

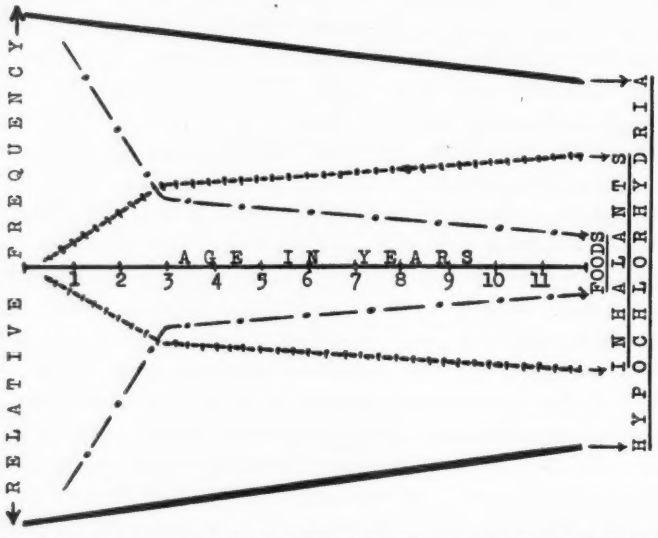
Secondly, a chemical effect. Fats and oils are known inhibitors of gastric secretion, and are used therapeutically for this purpose. One wonders whether the high fat diets—butter, cream, eggs, grade A milk, cod liver oil, and various emulsions—with which ill children are inundated, even if not bearing a direct aetiologic relationship, may yet exert some auxiliary baneful effect. In addition, may not the reputed effects of glucose in many cases be due to a balancing of the diet and a lessening of these inhibitory foods.

Thirdly, an innate effect. The greater frequency of hypochlorhydria in the younger children, as well as the tendency for the acid content to rise as age advances, suggests the possibility of some developmental defect of the gastric glands or some innate quality which hinders these children developing the power to secrete acid as early in life as normal children. The presence of a similar deficiency in a percentage of the parents also suggests that this may be a transmitted characteristic.

Fourthly, a pathologic effect. Following severe illnesses, bowel diseases, and exanthemata deficient secretion is an acknowledged fact. A chronic gastritis frequently complicates or succeeds one of these conditions, and the onset of asthmatic attacks is often assigned to such an illness. Hurst inclines to this view in adults, and in many of these achlorhydrics normal acid secretion may be restored by repeated gastric lavage over long periods. In children this is

a more difficult procedure and, in my experience in a few cases, not always attended with the good results that Hurst describes in adults.

Fifthly, a conservative effect. The hypochlorhydria is so frequent because the blood has so little acid-forming material to spare. Our recent biochemical investigations of the blood would seem to show that these asthmatic children have a great tendency to store up much alkali reserve, and all the acid ions are required to maintain the acid base equilibrium.



GRAPH 3. Schematic representation of relative frequency and inter-relationship between hypochlorhydria, food, and inhalant sensitization during the first decade.
Note :—(*a*) decreasing incidence of hypochlorhydria towards puberty ;
(*b*) rapid decrease in frequency of food sensitization after infancy ;
(*c*) gradual acquisition and increase of inhalant sensitization.

(*c*) *Is deficiency of secretion a cause or result of allergy?* This query is most significant, and, at present, a poser most difficult to answer. Most facts seem to point to an etiologic relationship, the inference being that, with insufficient acid, protein digestion cannot take place adequately, if at all, and thus large amounts of undigested protein with their accompanying 'reaction-producing substances' can be absorbed. Experimenters have shown that this is a usual process to a small degree in normal infants with a normal secretion ; that in the absence of acid secretion the gastro-enteric tract is even more permeable ; that foods largely partaken of by the nursing mother may be excreted, but slightly changed, in the breast milk, and be present to sensitize the child during the breast-feeding period (Donnally) ; and that, even in a normal person, the rapidity and intensity of the Prausnitz-Kustner reaction varies greatly according to the acid content of the stomach. In addition, this hypochlorhydria is most marked at the period of life when food sensitivity is at its maximum, and declines as age increases and inhalant sensitization takes its place. The

inter-relationship of these facts is portrayed in Graph 3. Were the hypochlorhydria a result of the allergic condition one would expect the deficiency to become more prevalent and extensive as age advanced and the disease progressed, but this is not so.

The author has shown in a previous publication that in about 70 per cent. of cases the tendency to manifest some form of allergic response is an inherited characteristic. Its ultimate establishment depends on other environmental and constitutional factors. One out of every four cases of allergy has had its onset during the first decade, and even in the allergies of later life the history of some manifestation during infancy or childhood is an extremely frequent and important observation. For these reasons one feels justified in suggesting that this hypochlorhydria of early life affords one channel through which this inherited tendency either becomes or is assisted in becoming an established fact.

(*d*) *Extent of influence of this hypochlorhydria.* Up to this stage the main discussion has centred around food allergy. Naturally one wonders whether hypochlorhydria is a concomitant feature of inhalant and bacterial sensitization as well. In grouping the results according to the chief type of protein giving the chief positive skin reaction, the incidence of hypochlorhydria is almost as frequent in inhalant as in food cases. It has also been noted in a few cases tested in the pre-asthmatic stage, and so outlines a preventive therapy. In Graph 3 an attempt has been made to represent pictorially this association between hypochlorhydria, food, and inhalant sensitization during the first decade. One notes the decreasing incidence of hypochlorhydria towards puberty, the rapid decrease in the frequency of food sensitization after infancy, and the gradual acquisition and increase in inhalant sensitization.

(*e*) *Empirical relationship.* An empirical relationship between hydrochloric acid and allergy is suggested in several literary references of extreme interest bearing on this question.

(i) Choremis undertook an investigation to determine a possible relationship between allergy and acidosis. Three children were selected who were shown to be sensitive to tuberculin repeatedly. Hydrochloric acid was given them in daily increasing doses of 4 to 30 drops for a period of 3½ months. During this period of acid metabolism there was a distinct lessening of the allergic symptoms, manifested both by a decrease in the size and duration of the tuberculin reaction and by a decrease in infiltration. After acid therapy in asthmatic children the author has found a lessening of previous definite skin reactions both to foods and inhalants.

(ii) Hemingway gives experimental evidence that sudden and repeated exposure of sensitized tissue to slight changes toward the alkaline side is extremely effective in bringing about exaggerated responses, and parallel with this increased sensitivity runs an exaggerated response to adrenalin. Addition of hydrochloric acid to the perfusing fluid reduces this sensitiveness, but further alkali again increases it, the action being reversible.

(iii) Von Kapff, from experience in factories manufacturing and employing acid gases, observed that the inhalation of volatile acids had not only an influence on the air passages and lungs, but also on the general circulation and metabolism, leading to better appetite, sounder sleep, and increase of weight. This led Hotz to try the inhalation of hydrochloric acid gas in definite concentration as a therapeutic agent in fourteen patients who had asthma or asthmatic bronchitis, the majority of whom were children. Nine recovered permanently, as relapses did not occur, and three showed improvement. The air containing the acid gas particles can be inhaled for some hours each day through a mask, or bowls of acid can be exposed in the sleeping chamber each night from three to four months.

(iv) Prausnitz-Kustner reaction. This reaction employs the principle of passive local sensitization as its basis. By the intradermal injection of serum taken from a hypersensitive person it is possible to passively locally sensitize a normal person to the causative proteins. Upon the ingestion or local inoculation of these proteins by the normal person injected, a wheal develops in the sensitized area in from a quarter to half an hour, indicating the absorption into the circulation of proteins in an undigested form. Walzer and his collaborators have used this reaction as a diagnostic procedure and perfected it in a large series of cases. They have shown that the rapidity and intensity with which this local reaction follows the ingestion of the causative allergen depends to a great extent on the acid content of the stomach of the recipient. Hypochlorhydria accelerates this reaction, hyperchlorhydria retards it.

Skin reactions are local nerve reflexes—since cocainization prevents their appearance—so one wonders whether, in the presence of a hypochlorhydria the nerve endings are in a more sensitive or susceptible state; or whether the hypochlorhydria is only concerned with regard to the form and rapidity with which the protein reaches the site of reaction; or whether the cause lies further back still in a slight alkalinity of the blood leading to the exaggerated responses experimentally produced by Hemingway.

At all events, numerous experimenters have shown that a definite relationship does exist between the state of hypochlorhydria and the degree of sensitivity evidenced.

VIII. *Therapeutic Indications.*

In the previous paragraphs the possible aetiologic significance of this hypochlorhydria has been discussed. Of equal importance are the therapeutic indications. To compensate for this deficient secretion it was decided to give hydrochloric acid by the mouth before or during meals, together with pepsin and a little syrup of senna to regulate the bowels. Commencing with a few minims of hydrochloric acid (B.P.), the dose was gradually increased until the optimum dose appeared to be from 20 to 30 minims three times a day. In achlorhydrics the dose has been even 60 to 90 minims.

The rapidity of progress depends on whether the offending allergen, as determined by skin tests, is removed at the same time, especially if it is of an inhalant nature.

(*a*) With acid therapy, plus the removal of the chief offending allergens as determined by skin tests, there is an immediate improvement in appetite, weight, sleep, and freedom from attacks. If the medicine is continued for some months, preferably till over the following winter, the child remains quite free, and then the medicine may be discontinued without further recurrence.

(*b*) With acid therapy alone there is an immediate improvement in appetite, together with an increase in weight. The average gain is from one to two or more pounds a month—ten pounds have been gained in three months. Sleep is much sounder, but slight attacks recur, which become of progressively shorter duration, of lesser intensity, and of diminished frequency. After three or more months, depending on the initial severity of the case, the attacks cease. The child then appears perfectly well whilst taking the medicine, but should this be stopped, or a slight infection supervene, milder attacks are liable, in some cases, to recur.

This therapy has been employed in several hundreds of cases of asthma during the last eighteen months, together with routine skin testing, especially for epidermals of animals, and the majority have been free from attacks for the past year. Others have been free for two or three quarters. After the attacks cease all are asked to report at the hospital for record purposes at quarterly intervals. By these means it is hoped that the progress will be kept on record and a further résumé of the results will be possible at a later date.

Since these investigations were undertaken the author has searched the literature for references to the employment of hydrochloric acid in the therapy of allergic conditions. Its use has been advocated occasionally. In the treatment of hay-fever, Bishop (1897) is reputed to have recommended its use. Lockard (1903), in discussing the treatment of hay-fever, states: 'In all cases I administer nitro-muriatic acid . . . and in only a few cases has it completely failed'. Of 27 cases treated during the summer of 1901, 24 were almost completely relieved. Beckman (1927) revived this treatment, and obtained 100 per cent. symptomatic cure in a series of 17 cases of hay-fever by the oral administration of nitro-hydrochloric acid. More recently (September 1930) he has collected together the results obtained in 237 cases treated by 34 physicians, each using the remedy for the first time. Of this number 160, or 67 per cent., obtained complete or marked relief of symptoms. Von Kapff's observations on asthma and influenza amongst employees of firms manufacturing or utilizing acid gases have been conducted since 1910, and it is of interest to note that he was a Professor of Chemistry and not a medical man. Hotz, hearing of these observations, carried out his investigations into their therapeutic effect in asthmatic children during 1929. Criep and McElroy (1928) observed that acid therapy had improved occasional cases of urticaria. Scheer (1928) reports success in the treatment of eczema of infants and young children by administration

of milk acidified with hydrochloric acid. Two series are reported, of 6 and 14 cases respectively, in which this treatment had excellent effects.

The author is applying acid therapy to all cases of allergy in which a hypochlorhydria is determined by gastric analysis.

Conclusions.

1. Asthmatic children, in general, show a diminished power of secreting acid gastric juice in response to a test meal as compared with normal children.

2. The important aetiologic and therapeutic indications of this deficiency are outlined.

3. The respective advantages and disadvantages of the oatmeal gruel and alcohol meals in children are discussed and the results compared.

I desire to express my sincere thanks and appreciation to the Honorary Staff of the Hospital for Sick Children, Great Ormond Street, London, for permission and assistance in investigating cases under their charge; to Dr. A. F. Hurst for many helpful criticisms and advice; to Dr. W. W. Payne for much aid and guidance in the biochemical technique; to Sisters Drayton and Hallam and Staff-Nurse Slatford for much assistance in the performance of the tests; and to the Asthma Research Council, by whose grant this work has been rendered possible.

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A RADIOGRAPHIC STUDY OF THE CORONARY ARTERIES IN HEALTH AND DISEASE[1]

By E. WYN JONES

(From the Pathological Department, University of Liverpool, and the Heart Department, Liverpool Royal Infirmary)

With Plates 9 to 15.

Introduction.

The primary aim of the investigation was to study the coronary system in disease, and if possible to correlate the pathological lesions found clinically and at post-mortem examination with changes in the vascular system. A thorough knowledge of the normal anatomy, the variations, anastomoses, and radiological appearances of the healthy coronary arteries is necessary before one can diagnose their pathological states. Brief accounts of the technique and the normal anatomy are given. Anatomical variations, the blood-supply of the valves, and the neuro-muscular tissue are considered. Finally, cases of interest with the radiological and microscopical findings are described.

Study of the blood-vessels aided by injection dates back to the middle of the last century. At the dawn of roentgenography attempts were made to inject radiologically-opaque material into the vessels, which were subsequently X-rayed. There is some doubt as to who was the first worker in this field, but Fryett (1) was the first to study the coronary circulation by this method. Since that time many types of injection masses have been used. I have prepared some of the injection masses in the exact way described by their discoverer and found them unsatisfactory.

The method of injection has become more complicated in an effort to obtain a standard technique and to rule out 'the human factor'. The old method of injecting by means of a syringe directly into the vessel has been entirely displaced. Gross (2) introduced a standard technique in 1921; later on, in 1927 (3), he published a description of a still more elaborate method. My aim was to find a simpler and an equally satisfactory injection technique, and the method described has the advantage of simplicity of design and ease of manipulation. The injections have been satisfactory.

[1] Received October 30, 1930.

Technique.

Radiologically pure barium sulphate as prepared by the British Drug Houses Ltd. was suspended by means of tragacanth as follows:

Barium sulphate .	50 grm.
Pulv. tragacanth Co. .	3 grm.
Thymol . . .	0·5 grm. dissolved in 5 c.c. of distilled water.
Distilled water .	70 c.c.

The Pulv. trag. Co. is rubbed up with 30 c.c. of distilled water. It soon becomes of the consistency of thick paste. The barium sulphate is added slowly —about 3 grm. at a time—and triturated thoroughly. This is continued until all the barium sulphate has been added, and at the end of thirty minutes a homogeneous mass, rather like cream, is obtained. At this stage the solution of thymol is added. The secret of success is the constant trituration and the slow addition of barium sulphate. The remainder of the distilled water is added slowly over a period of five minutes, while the trituration is maintained.

The apparatus (Pl. 9, Fig. 1) consists of a receptacle for the injection mass, mercury, manometer, pump, cannulae, connexions, and pinchcock.

As much as possible of the ascending arch of the aorta, the pulmonary artery, and the great veins are removed attached to the heart. Neglect of this precaution leads to leakage of the injection mass from the vasa vasorum and the auricular vessels. The heart is thoroughly washed to remove all clots from its cavities, and kept in normal saline at room temperature for twenty-four hours.

The coronary arteries are freed from the connective tissue surrounding their origin, and two ligatures are passed under each as near the aorta as possible. A small plug of wool is placed in the opening of the coronary sinus to prevent any of the mass finding its way accidentally into the venous system. The actual injection presents no difficulties. Pressure is raised in the receptacle by means of the pump until the mass begins to escape from the cannula. The pressure tubing is immediately clamped. By this means all air bubbles are displaced from the tubing. The cannula is passed down the aorta and into the opening of the coronary artery. It is fixed in position by tying the first ligature, and the heart is suspended on a tripod. The pressure is raised to 200 mm. and the pinchcock is released. The superficial branches may be seen filling immediately. The pressure is raised at once to 240 mm. and maintained for four minutes. The tubing is reclamped and the second ligature is tied. The pressure in the apparatus is reduced by means of the suction screw of the pump. The process is repeated on the other coronary artery. The heart is packed with wool and kept in formalin for twenty-four hours before being radiographed. It is returned to formalin for a further four days before the septum is dissected out and radiographed.

It was not considered advisable to inject both coronary arteries simultaneously as routine, although it was done in a few cases. The apparatus can be easily modified for this purpose by putting a Y-piece glass-connexion between the pinchcock and the cannulae. The objection is that in some cases where the anastomosis is exceptionally free one coronary may be filled as the other is being injected. If both vessels were injected simultaneously, this observation could not be made.

In the study of coronary anastomosis an attempt was made to inject masses of different radiological opacity into each coronary. However, it was found that although the difference in opacity was well marked in the larger vessels, it became almost negligible in the arterioles. Moreover, although masses of different opacity were easily prepared, the difficuty of obtaining masses of equal penetrability was very great. Masses of unequal penetrability, that is, not entering arterioles of the same size under identical conditions, were valueless.

In many cases microscopic examination of the myocardium and the vessels was performed.

Summary of the Normal Coronary Distribution.

In the investigation of eighty hearts by the method described, the findings agree in the main with those of Gross (2), so that it is not proposed to describe the normal anatomy at this juncture. The usual distribution may be summarized thus:

The right coronary artery supplies the anterior surface of the right ventricle except just at the apex. It supplies the right margin, and the posterior aspect of the heart as far as a point halfway between the crux and the left margin, the right auricle and the right posterior musculus papillaris.

The left coronary artery supplies the anterior surface of the left ventricle and the apex of the right ventricle, the left margin of the heart and the posterior aspect of the left ventricle as far as a point halfway between the left margin and the crux.

The following areas are jointly supplied by both coronary arteries in normal hearts: (1) The roots of the aorta and the pulmonary artery. (2) The lower third of the anterior surface of the right ventricle. (3) The auricular and ventricular septa. (4) The left auricle. (5) The right anterior and the left posterior papillary muscle. (6) Aortic cusp of mitral valve sometimes. (Pl. 10, Figs. 3 and 4.)

Blood-supply to the Valves.

The question of the blood-supply of normal valves is of more than academic interest, as it is of clinical significance in relation to the route of infection in valvulitis. Bayne Jones (4) was the first to show conclusively that normal valves contained blood-vessels. In the present series 15 per cent. of cases showed blood-vessels in the valves. Of these, two-thirds were in the mitral, and one-third in the tricuspid valve. In the case of the pulmonary and the aortic valves a fine network of vessels along the attached bases of the cusps was found, but in none of the cases did the vessels enter the cusp. Bayne-Jones found minute vessels in the pulmonary cusps 'extending as a hedge-like plexus' for about half the extent of the valve.

Kerr and Mettier (29), using Indian ink in their studies on the pig's heart, showed a very close vascular network in the auriculo-ventricular valve and the chordae tendinae. I found the barium sulphate suspension used in this series very satisfactory for showing up the arterioles and the coarser capillaries in the valves of the human heart, that is, it showed admirably the general scheme of the vascular architecture. In a number of pigs' hearts injected with barium at the beginning of this investigation the chordae tendinae and the auriculo-ventricular valves constantly showed a fairly rich vascular network. Judging from the excellent photographs of Kerr and Mettier there is no doubt however that the Indian ink preparation is capable of entering finer arterioles than the barium salt suspension.

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In the present series of injected valves, one was the seat of acute endocarditis, and three showed macroscopic evidence of chronic endocarditis. The remainder of the cases appeared normal, and there was no history or clinical evidence of acute rheumatism or scarlet fever or any of the other causes of acute endocarditis. The valve most easily injected is the aortic cusp of the mitral, and it derives its vessels from the branches in the auricular septum. Its vascular architecture may be divided into two groups—the complete type and the incomplete type. In the first type, which occurred in one case only, three distinct vessels enter the base of the valve, one anteriorly, one posteriorly, and an intermediate vessel about half a centimetre in front of the posterior vessel. These vessels pass downwards in the substance of the valve, and small branches, easily seen by means of a hand lens, are visible in all parts of the valve, arise from the main arterioles. The three vessels intercommunicate and terminate just above the line of closure of the valve (Pl. 11, Fig. 5). In the incomplete type there is one vessel present in all cases. It descends practically to the line of closure in each case, and small twigs are sent to the adjacent portion of the valve. The posterior vessel, mentioned above, is the one usually present (Pl. 11, Figs. 6 and 7). Heart valves contain blood-vessels up to the fourth month of foetal life. Thereafter the blood-vessels usually disappear completely before birth. It was found in a small series of cases that 13 per cent. of infants' hearts showed blood-vessels in the valves—a figure which approximates that of adults. This suggests that the presence of normal vascularized valves in the adult is possibly due to a persistence of the foetal state. If the persistence is only partial, one obtains the incomplete type of vasculature.

Blood-supply to the Neuromuscular Tissue.

The main source of blood-supply to the sino-auricular node is the ramus ostii cavae superioris. Its origin is from the right coronary artery in 54 per cent. of cases, usually fairly close to its commencement. In 46 per cent. of cases the artery to the *s.-a.* node arises from the left coronary, but, in spite of the variable origin and course, a number of its branches always terminate in the sino-auricular node, where it usually anastomoses with the lateral branch of the right circumflex artery.

The opening of the coronary sinus is encircled by a network of fine arterioles which arise from the auricular branches of the right coronary at the crux. The circle is usually completed by the auricular branch of the artery to the *a.-v.* node and the terminal twigs of Kugel's artery. The artery described by Kugel (5) arises from the commencement of the left coronary, passes into the auricular wall and into the base of the interauricular septum for a variable distance. The anterior portion of the node as it extends towards the undefended space is supplied by one or two twigs from Kugel's artery, but most of its blood-supply is derived from the artery to the *a.-v.* node which is in close apposition to it. The bundle of His, resting on the fibrous septum, has an

abundant blood-supply. The most important vessel is the specific artery to it—the ramus septi fibrosi. In addition, a large branch—also from the right coronary, about an inch below the ramus septi fibrosi, called the ramus ventriculorum superioris—sends branches upwards to the bundle. In a few cases a vessel, first described by Campbell (6), descends in the crista supraventricularis from the commencement of the right coronary artery to the undefended space. From the left coronary a slender vessel skirting the lower border of the crista supraventricularis reaches the fibrous septum, and immediately below the large septal branches send ascending vessels to complete the plexus. On rare occasions, the artery to the *s.-a.* node may furnish a vessel to this region. The anastomosis on the fibrous septum is free.

Vessels from this plexus accompany the right limb of the bundle for a short distance, and then a fairly large vessel from the large septal branch of the left coronary accompanies the bundle in the moderator band to the right anterior papilla and the adjacent portion of the right ventricle. The terminal portion of the right limb may receive a few arterioles from the anterior descending vessels of the right coronary artery. However, for all practical purposes, it may be stated that the left coronary supplies the right limb of the conducting tissue. The left limb of the bundle has no specific branch in the sense that the artery of the moderator band is specific to the right limb. It is supplied by the small arterioles in its neighbourhood, while its final ramifications like those of the right limb is supplied by the subendocardial capillary plexus.

Anastomosis and Age Change.

Two types of anastomosis occur in normal hearts. A. Between branches of the same coronary artery. B. Between branches of the opposite coronary artery. Type A is more marked in the left ventricular wall, but occurs to a lesser extent in the right ventricle and the auricles. Type B occurs: (1) In adventitia of the roots of the aorta and pulmonary artery. (2) Anterior surface of the right ventricle in its lower third. (3) The interauricular septum, especially at its base. (4) The interventricular septum—the area of best developed anastomosis in the heart. (5) The right anterior and the left posterior papillae. (6) The aortic cusp of the mitral valve on very rare occasions. The anastomosis between the coronary artery and the arteries in neighbouring organs was not investigated.

These anastomoses are present in normal adults' hearts, but become much more marked with increasing age and in disease of the myocardium and the vessels. Their increase after middle age is so marked that it appears as if the coronary system is preparing itself to deal with the obstructive lesions so frequently found after 60 years of age. Investigators (2 and 6) have demonstrated cases in which one coronary has been completely occluded close to its orifice, and yet it was filled through the anastomoses by injection of the opposite coronary. In one case of this series, the right coronary was immediately filled

as the left was being injected (Pl. 11, Fig. 8). The heart was from a person, aged 66, and there was no gross obstructive lesion of the coronary arteries. This is an important observation, as it shows, even more clearly than the cases mentioned, the extent of the anastomosis at this age. It appears to be constantly patent, because it did not require time to open the anastomotic channels. It is clear that the risk of degeneration of the myocardium following coronary occlusion is greatly diminished in a case of this type.

As the right ventricle preponderance diminished from the birth onwards, and the left ventricle gains ascendancy, a similar change is taking place in the vascular architecture. At birth the vascular arrangement is essentially the same as in the adult, but both ventricles are equally vascularized. The vessels are straight and tend to be superficially embedded in the myocardium; the anastomosis is negligible (Pl. 12, Fig. 9). The rapidly increasing preponderance of the left ventricle is accompanied by a corresponding increase in its blood-supply; there is an appreciable septal anastomosis (Pl. 12, Fig. 10). At 30 the arteries commence to become tortuous, the septal anastomosis is very definite, and there is a well-marked diminution in the vascularity of the right ventricle. At the age of 50 tortuosity is marked, the increase of the subpericardial fat is accompanied by an increase in the minute vessels to the fat—the rami telae adiposae; coronary anastomosis is well marked. By the age of 60 all the distinctive features of the previous decade are exaggerated, and a large percentage of cases reveal definite evidence of coronary sclerosis. The diminution in the vascularity of the right ventricle and free anastomosis are easily demonstrable (Pl. 12, Fig. 11). The wasting of the body in persons over 70 is often accompanied by a certain degree of atrophy of the heart, and this increases the tortuosity of the vessels. All the other changes become more pronounced. These findings agree in the main with those of Gross, but they differ in one important detail. Gross states that 'in the second decade the distribution of blood is beginning to be a little more marked on the left side', and 'in the third decade life shows a definite, though not yet marked, left-sided vascular predominance'. In the present investigation, definite predominance of the left-sided vasculature was found at the age of six months (Pl. 12, Fig. 9 *a*), and it gradually increased, becoming well marked at 10 years of age, which is much earlier than in the cases investigated by Gross. The findings are in agreement with the recent work of Whitten (19) who used a modification of the celluloid corrosion method (20).

Anatomical Variations.

The study of a large number of hearts reveals the fact that the coronary circulation is subject to many variations. They are all of anatomical interest, and many are important in the elucidation of clinical and autopsy findings. The latter group only will be discussed here. Cases have been described where only one coronary artery was present, but they are excessively rare. Three coronary arteries occur more frequently than is usually recognized. In this series, the accessory vessel was on the left side in one case, and in the remaining eight

cases it arose on the right side. The accessory left coronary supplied the antero-lateral aspect of the left ventricle. In all the cases, the right accessory coronary artery arose from the right anterolateral sinus of Valsalva close to the orifice of the main vessel, and supplied the anterior surface of the right ventricle. The accessory vessel may be of importance as a source of free anastomosis as shown by the following case. In the only case of coronary thrombosis which possessed an accessory coronary artery in this series, the accessory vessel was injected first. The whole of the left anterior descending branch and its septal branches as far as the lower level of the thrombus were filled from this small vessel. Wide anastomotic channels were easily visible (Pl. 14, Fig. 18).

The coronary artery reaching the crux is one that gives rise to the specific artery to the *a.-v.* node. In cases where the crux receives a double supply, that is, where it is reached by the right and left circumflex arteries, this statement has to be modified. In 83 per cent. of cases the artery to the *a.-v.* node arises from the right coronary artery at the crux. It is of no clinical significance whether it arises from the circumflex or from the commencement of the descending branch in the posterior interventricular groove. In the remaining 17 per cent. it arose from the left circumflex. In 11 per cent. of cases of the present series, both circumflex arteries reached the crux; in these cases the ramus septi fibrosi was given off the right circumflex except in two instances.

It is important to note that in 15 per cent. of hearts the left coronary artery is responsible for the entire blood-supply of the ventricular septum. By this is meant that the left coronary gives rise to the anterior and posterior interventricular vessels, and that branches of these vessels supply the septum. In 60 per cent. of cases of this group, the artery to the *s.-a.* node arose from the right coronary, while in the remaining 40 per cent. it arose from the left coronary. The significance of this finding is that in 5 per cent. of all hearts the entire neuromuscular tissue is supplied from the left coronary artery (Pl. 13, Fig. 12), and in about 10 per cent. the sino-auricular node is supplied from the right coronary, while the remainder of the neuromuscular tissue is solely supplied from the left coronary artery (Pl. 13, Fig. 13).

In the 15 per cent. of cases where the left coronary artery supplied the crux the right coronary was a small vessel and did not extend beyond the right margin of the heart. In view of the fact that the left anterior descending branch is present in 100 per cent. of cases, it cannot be said that the right coronary may be the sole blood-supply of the septum in normal hearts. However, in the case of complete occlusion of the upper portion of the left anterior descending artery already mentioned it was demonstrated that the septum was almost entirely supplied from the right coronary artery.

The Coronary Arteries in Disease—Coronary Sclerosis.

The coronary arteries bear an important relationship to the structural and functional changes in the heart inasmuch as the integrity of the myocardium is dependent on an adequate blood-supply. The manifestations of coronary disease are protean, but there may be complete absence of symptoms, so that it is sometimes difficult to assess the part played by coronary disease in the production of the clinical condition.

It is clear that obstructive lesions of the coronary arteries lend themselves to easy demonstration by the radiographic method, and it is in this particular branch of the work that most important information is obtained, although interesting findings in relation to the general arrangement of the vascular field

have been noted; for instance, marked relative increased vascularity of the left auricle was found in cases of mitral valve lesions.

The obstructive lesions of the coronary arteries are embolism, arteriosclerosis, and thrombosis. Embolism is by far the most uncommon cause of coronary occlusion; the usual origin of the embolus is from a valve that is the seat of subacute infective or malignant endocarditis.

Sclerosis of the coronary arteries is very frequently met with in persons over 50, and most of the cases do not present any clinical signs or symptoms to indicate its presence. The incidence of sclerosis increases with increasing age. Of all the cases over 50, definite radiological evidence of sclerosis was found in 40 per cent.; between 50 and 60, it was found in 30 per cent.; while between 70–75 it was present in 80 per cent. of cases. The age incidence of atheroma of the aorta closely approximates that of coronary sclerosis, and the lesions usually coexist; yet in some cases showing advanced lesions of the aorta the coronary arteries were normal, and again, advanced sclerosis of the coronary arteries was found in association with an aorta that appeared healthy. In half of the cases of coronary sclerosis marked left ventricular hypertrophy was found, but in all these cases with hypertrophy there was macroscopic evidence of chronic interstitial nephritis. Coronary atheroma may cause a certain degree of hypertrophy by proliferation of fibrous tissue—this is a false hypertrophy. If marked left ventricle hypertrophy is found there is some other factor, in addition to coronary disease, to account for it. The extent of the sclerosis varies greatly—all gradations from a small plaque to calcification of all the main vessels may be found.

The usual site of the sclerosis is the left anterior descending artery. The change is most marked in the first inch, becomes less marked in the second inch, and the vessel gradually becomes more or less normal. Sclerotic changes in the left circumflex are associated with it. In most of the cases in this series the right coronary has not been affected, but if the disease is advanced in the left coronary there is usually radiological evidence of early changes in the right coronary artery, especially in the circumflex branch. In one case the right coronary artery was almost occluded by an atheromatous plaque, while the left coronary was fairly normal.

The radiological appearances of sclerosis are characteristic. The affected vessel is usually straight, and this is often a marked contrast to the tortuosity of the vessels in its neighbourhood. The outline of the vessel is irregular and the branches are nipped just beyond the point where they leave the parent vessel; they appear as if they had been lightly ligatured. Marked variations in the diameter and in the intensity of the opacity of the affected vessel are found. In advanced cases a peculiar 'chipped' appearance of the outline, rather like the over-riding edge of bone in a spiral fracture, is noticed. The nipping of the branches and variations in diameter are due to a moderate degree of sclerosis, while variations in the opacity and 'chipped' appearance are due to advanced lesions with calcification. A vessel may show all these

features in series, the commencement of the vessel showing advanced sclerosis and calcification, while farther along its course the vessel may show a moderate degree of sclerosis gradually merging into the normal vessel. Where there is associated chronic interstitial myocarditis there is a loss of the finer vascular elements due to their strangulation by fibrous tissue (Pl. 13, Fig. 14). The radiological appearance may be complicated by superimposed thrombosis.

The effects of coronary sclerosis may be briefly summarized as follows: (1) There is often complete absence of signs and symptoms, the condition being only found at the autopsy. (2) It is the commonest pathological finding in cases of angina pectoris. (3) Impaired nutrition of the myocardium leads to fibrous myocarditis with its attendant symptoms. Rupture is an unusual termination. Locke (7) analysed seventy-one cases of rupture of the heart; Goodall and Weir (28) describe fourteen cases. Their findings may be summed up thus: The condition is usually found in men between 60 and 70; the site of the rupture is the anterior surface of the left ventricle near the apex. The coronary arteries are calcified in most of the cases, but superimposed thrombosis is uncommon. (4) Atheroma increases the liability to thrombosis. The thrombosis may occur at the usual site of the atheroma, the damaged intima providing a suitable surface for the beginning of the process. The thrombosis may also occur in the finer arterioles distal to the area of atheroma. This is due to sclerosis in the finer vessels and stasis due to diminished pressure beyond the obstruction in the main trunks. (5) Symptoms and signs of coronary thrombosis may occur where there is marked atheromatous constriction of the artery (Wearn (8)), although there is no evidence of thrombosis at the autopsy. (6) Arrhythmias are somewhat uncommonly found due to coronary sclerosis. Right branch bundle block is very much more commonly found than the left-sided lesion, and this is due to the fact that the right limb of the bundle derives its blood-supply from the portion of the left coronary artery most liable to sclerosis.

Coronary Thrombosis.

The study of coronary thrombosis is a branch of cardiology that has come to the fore in comparatively recent years. Herrick (9), in 1912, collected a series of cases and correlated the clinical and autopsy findings. It was realized that the disease was not invariably fatal, and Levine (10) described five cases with recovery. Since then a great deal has been written on the condition. Sutton (11) and Reisman (12) have contributed further, and Levine (13) has published an excellent monograph on the subject. Coombs (14) emphasizes the fact that coronary thrombosis is much more frequent in private than in hospital practice, while McNee (15) suggests that the condition may be more common in America. Still more recently Bramwell (16) has discussed the clinical findings, and Herapath and Perry (17) demonstrated the familial tendency to arterial degeneration and sudden death at an early age.

In nearly all the cases of coronary thrombosis there is underlying sclerosis; therefore, as one would expect, the usual site of thrombosis is the left anterior descending branch. However, no part of the coronary system is immune. The immediate result of occlusion is the formation of an infarct, rather less in size than the area of myocardium supplied by the occluded branch, because the coronary anastomosis is sufficient to maintain the nutrition of the periphery of the infarct. The portion immediately adjacent to ventricular cavity may not necrose as the subendocardial capillary plexus may be sufficient to supply its needs. This infarct is of a pale yellow colour, soft and oedematous; a line of demarcation forms, cutting it off sharply from the unaffected muscle. It becomes mottled with small haemorrhages, and finally all that remains in a favourable case is a fibrous scar much smaller than the area of the original infarction.

The three main groups of complications—arrhythmias, intracardiac thrombosis, aneurysms, and rupture—have been fully analysed by Parkinson and Bedford (18) and by Levine (13).

The radiological appearance of a thrombosed vessel will naturally vary with the extent of the thrombosis. If complete occlusion has occurred, the affected vessel will not give a shadow on the X-ray film, and the portion of myocardium supplied by it will not show injected vessels. In many instances thrombosis is secondary to marked coronary sclerosis, and this if associated with calcification will give a shadow which is quite different from that cast by a normal injected vessel. If occlusion is incomplete, an attenuated indefinite shadow is seen, and this offers a marked contrast to the smooth even outline of the unaffected vessels. A thrombus in the process of canalization has a characteristic appearance. The affected vessel has an indefinite and irregular outline, appears double in parts, and the shadows are continually overlapping. If a considerable time has elapsed between the time of occlusion and the death of the patient it is probable that many anastomotic channels will have opened, so that the area of myocardium supplied by the occluded branch may contain injected vessels.

Clinical Cases and Radiographic Findings.

Paroxysmal tachycardia. Lewis has defined paroxysmal tachycardia as the sudden acceleration of the heart-rate in response to new impulses arising from a focus removed from the normal pacemaker—the sino-auricular node.

The etiology of the condition is often obscure, but it appears to be associated more commonly with rheumatic valvular disease than with any other lesion. Obstructive lesions of the coronary arteries may account for a number of cases, but comparatively few cases are described in the literature. Robinson (21) describes a case of paroxysmal tachycardia due to partial occlusion of the orifice of the left coronary artery by atheroma of the aorta. Robinson and Hermann (22) published four cases of paroxysmal ventricular tachycardia apparently due to coronary occlusion; post-mortem examination was done in

one case, and the diagnosis was confirmed. Parkinson and Bedford (18) found the condition in 2 per cent. of cases of cardiac infarction. Lewis (23) produced paroxysmal tachycardia in the dog by ligaturing a coronary artery.

The case in this series is of interest, as it provides another example of paroxysmal tachycardia associated with marked arteriosclerosis of the coronary vessels, which had appeared at an exceptionally early age.

Case 1. The patient, E. E., a housewife, aged 29, was admitted to hospital complaining of dyspnoea and palpitation—her third 'heart attack'. She was in the same hospital and treated by the same medical officer in the second and third attacks. She had exophthalmic goitre for the last two years but she was not a severe case. There was nothing relevant in the past history apart from the heart attacks. There was an interval of four months between the second and third attacks, and the patient was well during that period.

On admission during the second attack, the heart-rate remained regular at 220 a minute. Its rate was uninfluenced by treatment. The pulse-rate suddenly returned to normal in a few days, and the patient was discharged. The patient was fourteen weeks pregnant at this time.

On readmission, the heart-rate was again 220 and regular. Dyspnoea and general distress were present. The heart was enlarged, but the rate was too rapid to determine whether there were murmurs present. Oedema of the ankles and slight cyanosis appeared, and moist sounds were audible at the bases of both lungs. Abortion occurred at 30th week of the pregnancy. The dyspnoea increased, and in spite of rest and massive doses of tincture of digitalis the heart-rate was unaffected. The signs of cardiac failure became still more pronounced, and the pulse remained over 200. The patient died in a few days.

At the autopsy the heart was much enlarged, and the increase of subpericardial fat was so marked that there was practically no myocardium visible on the anterior surface of the heart. All the cavities of the heart were dilated, but there was no gross valvular lesion. The mitral ring was dilated, and the valve was relatively incompetent. There was no evidence of thrombosis or infarction. The foramen ovale was closed. There was a considerable degree of atheroma of the aorta, especially around the coronary orifices. The other organs showed evidence of congestion only.

In the radiogram, the anterior descending branch of the left coronary showed marked irregularity of outline, the 'chipped' appearance, and nipping of its branches for the first $2\frac{1}{2}$ inches of its course. The right coronary artery was normal. There was definite increased relative vascularity of the left auricle, probably associated with the mitral incompetence. There was diminished relative vascularity of the right ventricle. The septal vessels showed marked tortuosity and a loss of the finer vascular elements due to fibro-fatty changes in the myocardium. The radiogram, as a whole, presents the appearances of the coronary arteries in a person about 65 years of age (Pl. 13, Fig. 15 and Pl. 14, Fig. 16).

Microscopic examination confirmed the radiological diagnosis of advanced coronary sclerosis and calcification. Marked fatty infiltration and degeneration with some fibrosis was found in the ventricular septum and the right ventricle. The same changes were found diffusely in the auricles and in the region of the *s.-a.* and *a.-v.* nodes. The left ventricle showed the same changes to a less marked extent.

It was unfortunate that the case occurred in an institution where there was no opportunity of taking electrocardiographic records. She was seen by several physicians who agreed that the diagnosis was paroxysmal tachycardia. It was considered safe on clinical grounds alone to arrive at this diagnosis, because: (1) The patient had a pulse-rate of 200 and it was regular. (2) The

rate was unaffected by rest and digitalis. (3) The abrupt ending of the second attack. (4) The absence of any evidence of 2:1, 3:1, or 4:1 rhythm. Marked sclerosis of the coronary arteries at the age of 29 in a female is a very rare occurrence, and associated with the inadequate anastomosis it proved a great handicap to the efficient maintenance of the coronary circulation.

It is difficult to gauge the extent to which the exophthalmic goitre was responsible for the condition. Exophthalmic goitre is a common disease, especially in women at this age, but no references could be found to its association with paroxysmal tachycardia. Well-marked arteriosclerosis of the coronaries is so rare at this age that it is safe to conclude that it was the primary factor in the production of the arrhythmia, while the hyperactivity of the thyroid served to aggravate the condition. Death in the paroxysm was undoubtedly due to the extra strain of the last weeks of pregnancy on the heart.

Coronary occlusion. Case 2. The patient, W. G., a railway clerk, aged 55, was admitted to hospital, having collapsed in the street. As he was walking after lunch he suddenly felt faint, and was seized with severe pain and tightness in the praecordium. He collapsed and became unconscious. There was nothing relevant in the past history, and he had had no previous 'anginal' attacks.

On admission he was cyanosed and very dyspnoeic. The pulse was weak and regular—60 per minute. Temperature 96° F. The apex beat was in the fifth intercostal space and 4½ inches to the left of the middle line. The heart sounds were very faint and the blood-pressure was 85/75 mm. There were moist sounds in the bases of both lungs, and there was a moderate albuminuria. On the next day his general condition improved, and the pulse-rate rose to 100, while the temperature remained subnormal. The liver was enlarged 3 inches beyond the costal margin, and the amount of urine was diminished. The pain had almost disappeared, and the dyspnoea was the predominant feature. On the following day the dyspnoea was much worse and the moist sounds in the lungs were much more marked. The oliguria was very pronounced, and the non-protein nitrogen content of the blood rose to 60 mg. per cent. The patient died that evening.

At the autopsy, about a pint of clear yellow fluid was found in each pleural cavity. The air-passages and the lungs were intensely congested. The liver weighed 76 ounces and showed early nutmeg changes. The kidneys were congested, but there was no evidence of chronic nephritis. The heart weighed 17 ounces and the left ventricle was much hypertrophied. The left ventricle, from the base to the apex antero-laterally, was of a yellowish white colour, with areas of small haemorrhages on section. The portion immediately under the pericardium was not affected to the same extent as the deeper part of the muscle. There was no intracardiac thrombosis. The remainder of the heart was normal. The aorta and the coronary arteries showed many atheromatous areas, and there was a thrombus in the left anterior descending artery, which apparently closed its lumen. Unfortunately, it was impossible to obtain the heart for injection owing to medico-legal difficulties. Microscopically the left coronary artery showed an organizing thrombus with evidence of canalization; the lumen was almost completely occluded. The left ventricle showed well-marked fibrosis, and in one portion there was myomalacia cordis. The muscle-fibres were swollen and oedematous, appearing as if they contained coarse granules in their substance. The striations were not visible, and the nuclei did not stain at all in some areas, while in other areas they appeared small and shrunken. There was marked extravasation of erythrocytes and numerous small areas of polymorphonuclear leucocytic infiltration. The lungs showed intense oedema and congestion; many catarrhal or 'heart failure' cells were present in the alveoli.

Case 3. A labourer, W. C., aged 52, was admitted with a history of sudden pain in the praecordium and marked dyspnoea of a few hours' duration. History

of a somewhat similar attack years previously was given. The pulse was rapid and regular, and its tension was increased. The wall of the radial artery was palpable and he had a locomotor brachial artery. The apex beat was 5 inches out and in the sixth intercostal space. Gallop rhythm appeared soon after admission. Oedema of the ankles developed, the liver edge became palpable, and the dyspnoea increased. There were moist sounds audible in the bases of both lungs. Death occurred the following day.

At the autopsy, the enlargement of the heart was confirmed and there was marked hypertrophy of the left ventricle. There was no recent infarction, but there was a large area of fibrosis in the anterior portion of the septum and in the adjacent portion of the left ventricle anteriorly. The aortic cusps were thickened and the other valves were normal. All other organs were acutely congested and there was evidence of chronic interstitial nephritis.

The radiogram of the injected coronary arteries revealed advanced coronary sclerosis and calcification of the first 2½ inches of the left anterior descending artery, with almost complete occlusion of its lumen. The septal anastomosis formed an exceptionally close network. The opacity of the anterior portion of the septum is probably due to the dense fibrous scar (Pl. 14, Fig. 17).

Microscopically, an old-standing thrombus superimposed on an area of atheroma and calcification was found. The thrombus was organized, and many of the arterioles close to the main vessel were completely occluded by thrombosis and had become fibrous cords. There was no recent thrombosis. There was dense fibrosis, with small areas of lymphocytic infiltration in the septum and the left ventricle. In many areas the muscle was completely replaced by fibrous tissue.

Case 4. The patient, T. T., a musician, aged 52, was admitted to hospital complaining of intermittent pain in the left hypochondrium for three years. There was evidence of marked loss of weight. The facies was bluish red and the clinical picture was highly suggestive of polycythaemia vera. Examination of the blood confirmed this diagnosis. There was no clinical or serological evidence of syphilis, and at no time during the illness did the blood-platelets rise above 600,000 per c.mm. Just before death, the pain in the left hypochondrium became much more marked. The heart was normal throughout the illness.

At the autopsy, there was marked perisplenitis, and the spleen showed areas of old and recent infarction. The splenic artery contained a recent thrombus 1½ inches long. The liver showed areas of diffuse necrosis. The heart was somewhat enlarged, and the subpericardial fat was increased. The left ventricle was slightly hypertrophied, and the myocardium and the valves were normal.

The right accessory coronary artery was injected first and its branches anastomosed freely with the anterior descending branch of the left coronary, which was filled up to a point 2 inches from its orifice. The septal and the ventricular branches were filled from the small accessory vessels. The injection was then completed in the usual way. The right coronary artery contained a canalized thrombus, while the lumen of the left anterior descending vessel for the first 2 inches of its course was almost completely occluded by thrombosis (Pl. 14, Fig. 18, and Pl. 15, Figs. 19, 20). The radiological diagnosis was confirmed microscopically. There was no evidence of coronary sclerosis.

Comments.

It will be noted that three cases are in males between the ages of 50 and 60, and this is in accordance with the usual findings. It is interesting to note that in the first case there was complete absence of symptoms suggesting

coronary artery disease until the onset of the final catastrophe. The severe pain disappeared with the onset of the cardiac failure of the congestive type. The low blood-pressure is a common occurrence and is the explanation of the oliguria. The pericardial rub is frequently absent, as in this case; but when present it is diagnostic of infarction. This is the type of case that was first recognized by the earlier writers, who, for a time, did not clearly differentiate the condition from angina pectoris.

The second case conforms more or less to the unusual type described by Wearn (8), where all the signs and symptoms of acute coronary thrombosis occur in cases with marked narrowing of the lumen of the coronary arteries without recent thrombosis. It illustrates the end result of infarction with recovery from an attack, and the profuse septal anastomosis developed as a result of partial or complete occlusion of a main branch. Finally, it serves to emphasize the predisposition of such a case to further sudden coronary upsets.

In the last case, coronary thrombosis occurred very gradually, and there was adequate time for the establishment of an efficient collateral circulation. The radiogram of the canalized thrombosis of the right coronary artery, complete occlusion of the left coronary, the presence of an accessory coronary artery, and the absence of underlying sclerosis make it a case of unusual interest.

The following considerations may explain to a certain extent the varying manifestations of coronary thrombosis: (1) *Site of occlusion.* The occlusion of the artery to the auriculo-ventricular node is a much more serious lesion than the occlusion of a branch of a similar size on the lateral aspect of the left ventricle. (2) *Size of vessel occluded.* The larger the artery occluded the greater is the liability to intracardiac thrombosis, aneurysm, and rupture. (3) *Age and anastomosis.* Coronary anastomosis becomes much more extensive with increasing age. It is clear, therefore, that the coronary system of persons over 50 may be capable of adjusting itself rapidly to any sudden vascular alterations. (4) *Rate of occlusion.* Compensatory anastomosis is well developed when the rate of occlusion has been slow, and the myocardium is normal in those cases where occlusion has been very gradual. (5) *Blood-pressure.* Low blood-pressure tends to delay the opening of new anastomotic channels. (6) *Condition of the myocardium.* The presence of chronic interstitial myocarditis is a common occurrence prior to infarction, and it is due to the coronary sclerosis which existed prior to the final occlusion. The presence of fibrosis is serious in that the finer arterioles are obliterated, and thereby the anastomosis is much diminished (Pl. 13, Fig. 14). (7) *Canalization.* Canalization of the thrombus will assist to a certain extent in re-establishing the blood-supply.

The Vascular Basis of Heart-block.

Of the causes of heart-block, the most interesting at this juncture is the group in which stenosis of the specific artery to the *a.-v.* node and bundle—the ramus septi fibrosi—has led to the condition.

Neuhof (24) describes a case of complete heart-block and auricular fibrillation associated with complete calcification of the artery to the *a.-v.* node. The patient was acutely ill when admitted, but had been in normal health prior to admission. At the autopsy the ramus septi fibrosi was found to be calcified and the myocardium in the region of the *a.-v.* node was degenerated—'the zone of degeneration undoubtedly included the node'.

In view of the calcification, it is clear that the ramus septi fibrosi must have been occluded for a long time prior to the onset of heart-block. The free anastomoses in the region of the base of the auricular septum and the undefended space, the details of which have already been described, maintained an efficient blood-supply to the conducting tissues. As soon as the anastomoses proved inadequate the patient became acutely ill with signs of heart-block. This case again emphasizes the fact that slow occlusion of the coronary vessels is often latent for a long period of time.

Geraudel, Bénard, and Hillemand (25) describe in detail a case of Stokes-Adams syndrome and mention an exactly similar case previously published by them. In both cases there was almost complete occlusion of the artery to the *a.-v.* node, due to areas of atheroma, and accompanied by a certain amount of degeneration of the fibrous septum and the adjacent muscle, but the bundle of His was intact. Geraudel concludes by stating that necrosis of the fibrous septum and the neighbouring muscle is not incompatible with life, while the *a.-v.* node and bundle is a portion of the heart that does not necrose, because as soon as its blood-supply is materially interfered with the patient dies. In other words, the patient dies before there is time for necrosis of the bundle to appear. Geraudel and his co-workers formulated a theory which states that variations in the blood-supply to the *a.-v.* node leads to variations in the rate and rhythm of the heart. Stenosis of the specific artery and a consequent diminution in the blood-supply to the node leads to a slowing of the heart-rate, and possibly to dissociation of the auricular and ventricular rates in some cases.

Oppenheimer and Williams (26) mention a case of incomplete heart-block due to sclerosis of the specific artery to the *a.-v.* node, where the bundle of His was normal on examination. They concluded that 'heart-block without anatomical lesions in the auriculo-ventricular system may be of neurogenic or circulatory origin'. Libman (27) accepts Geraudel's hypothesis and states that he has evidence that sino-auricular block may be caused in the same manner.

It is clear from these cases that Geraudel's theory is feasible, but the extent and the efficiency of the anastomoses have been entirely disregarded. Partial occlusion of the vessels in other parts of the heart are often completely compensated for, and it is reasonable to suppose that in the region of the undefended

space the same conditions would obtain. If this theory is the full explanation, one would expect heart-block to be frequently met with in cases of coronary occlusion. Wearn (8) found two cases of heart-block in nineteen cases of coronary thrombosis. Parkinson and Bedford (18) found one case of complete heart-block and one case of incomplete heart-block in a hundred cases of cardiac infarction. In view of these findings, and the frequency with which coronary sclerosis is met with, it is clear that mere diminution in the blood-supply is scarcely an adequate explanation, otherwise heart-block would be of common occurrence. It is of importance to note that Neuhof's case and one of Geraudel's cases received very large doses of digitalis through an oversight. Neuhof's case was given 1½ ounces of tincture of digitalis in an hour, and the pulse-rate fell from 150 to 28 per minute in that time.

In one case of this series there was marked stenosis of the artery to the *a.-v.* node, but the vascular network in that region was normal (Pl. 15, Fig. 21). The heart was normal clinically. There is no doubt that occlusive lesions in coronary systems may cause heart-block even in the absence of microscopic changes in the neuromuscular tissues. It is difficult to understand how stenosis of the specific artery *per se* will materially diminish the blood-supply and so lead to heart-block, in view of the free anastomosis in the *s.-a.* and *a.-v.* nodes. The free anastomosis is the explanation of the infrequent association of heart-block and coronary occlusion and possibly the explanation of the return to normal rhythm of the cases where arrhythmia has followed the occlusion.

Conclusions.

1. A simple and reliable standard method of injection of the coronary arteries has been devised suitable for the study of the vascular structure of other organs, e. g. kidney and spleen.

Anatomical.

2. The coronary arteries are liable to many variations, a knowledge of which is of great importance in the study of diseases of the heart.

3. The anastomosis of the coronary arteries is free.

4. Increasing age produces characteristic changes in the vascular architecture, and the left-sided vascular predominance occurs much earlier than the age stated by Gross.

5. Normal valves, especially the aortic cusp of the mitral, contain blood-vessels.

6. The neuromuscular tissue is supplied by many alternative channels, and in a number of cases is solely supplied by the left coronary artery.

Pathological.

7. Atheroma of the coronary arteries is very common after 50 years of age, and it increases the liability to coronary thrombosis.

8. Coronary atheroma is an important but rather infrequent cause of cardiac arrhythmias (Case 1).

9. Coronary thrombosis is usually superimposed on coronary atheroma (Cases 2 and 3).

10. The usual manifestations of coronary thrombosis may be absent, thrombosis occurring in absence of symptoms, and the condition may only be found at the autopsy (Case 4).

11. Symptoms and signs of acute coronary thrombosis may occur where there is marked constriction of the lumen of one of the main trunks, without recent thrombosis (Case 3).

12. Variations in the clinical and autopsy findings in coronary thrombosis may be explained to a large extent on anatomical and physiological grounds.

13. In a case showing marked stenosis of the specific artery to the *a.-v.* node, there was no difference in the radiological appearance of the anastomotic plexus on the base of the auricular septum and the undefended space.

I have great pleasure in expressing my gratitude to Professors J. Henry Dible and John Hay and to Dr. H. Wallace Jones for many valuable suggestions; to Professor R. E. Kelly for permission to do the work during my tenure of the Thelwall Thomas Fellowship; to Dr. R. E. Roberts and the Staff of the X-ray Department of the Liverpool Royal Infirmary for their unfailing kindness and assistance.

I wish to thank the Medical Staff of the Liverpool Royal Infirmary, the Royal Liverpool Children's Hospital, and Walton Infirmary for allowing me to have post-mortem material and access to the records of the cases.

My best thanks are due to the editors of *The Practitioner*, who allowed me to reprint parts of the text and many of the figures (1, 2, 8, 14, 17, 18, 19, and 20) which appeared in their number of September 1930.

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Gross (2) and Whitten (20) give a very complete bibliography of technical methods of injection. Levine (13) gives a very complete list of references to literature bearing on coronary thrombosis.

DESCRIPTION OF PLATES.

PLATE 9, FIG. 1. The apparatus. The cannula is shown outside the aorta for the sake of clearness. It was actually passed down the aorta into the orifice of the coronary artery.

FIG. 2. The normal coronary arterial system of adult aged 45. The right coronary artery is to the left of the figure, as in all the figures that follow. Note (1) the position of the *s.-a.* node, (2) the artery to the *s.-a.* node arising from the right coronary, (3) the crux, (4) the posterior descending branch of the right coronary in the interventricular groove, (5) the right marginal branch, (6) the branch in the moderator band, (7) the left anterior descending artery.

PLATE 10, FIG. 3. Septum of the heart.

FIGS. 3 & 4. The interauricular and interventricular septa. These two figures together illustrate the anatomical facts described in the text. (1) Ramus septi fibrosi. (2) Ramus ventriculorum superioris. (3) Campbell's artery. (4) Ramus ostii cavae superioris. (5) The branches of the left coronary artery. (6) Kugel's artery. (7) Opening of the coronary sinus.

PLATE 11, FIG. 5. The complete type of vasculature of the mitral valve. Drawing of the actual injected specimen.

FIGS. 6 & 7. The incomplete type of vasculature of the aortic cusp of the mitral valve. Drawing and radiogram of injected specimens.

FIG. 8. Septum of the heart. The auricular vascular ring and the free anastomosis in the auricular and ventricular septa are well shown. In this case, the right coronary filled completely as the left coronary artery was injected. (1) Artery to the *s.-a.* node, (2) the auricular branch of (3) the artery to the *a.-v.* node, (4) Ramus ventriculorum superioris, (5) branches of the left coronary, (6) Kugel's artery.

PLATE 12, FIG. 9. The coronary arteries of a full term foetus. Both ventricles equally vascularized, i. e. a relative predominance of the right coronary artery.

FIG. 9*a*. Coronary arteries at the age of 5 months. Note the definite predominance of the left-sided vasculature.

FIG. 10. Coronary arteries at ten years of age.

FIG. 11. The coronary arteries of an adult aged 55. Note the diminished vascularity of the right ventricle and the early atheroma of the left anterior descending vessel (1).

PLATE 13, FIG. 12. The coronary arteries of an adult aged 66. The left coronary artery supplies the whole septum, and the right coronary artery is small. There is marked tortuosity of the vessels but no atheroma. Note (1) Ramus ostii cavae superioris arising from the left coronary artery ; (2) the left circumflex supplies the crux and posterior groove. The left coronary artery supplies the whole of the neuromuscular tissue.

FIG. 13. The coronary arteries of an adult aged 29, a case of splenic anaemia. The left coronary artery supplies the whole septum. Note the smooth, even outline of the vessels and the absence of tortuosity: (1) small right coronary, (2) the left circumflex artery supplying the crux and the posterior groove, (3) large lateral auricular branch, (4) artery to *s.-a.* node. The *s.-a.* node is supplied from the right coronary while the remainder of the neuromuscular tissue is supplied from the left coronary artery.

FIG. 14. Septum of the heart showing (1) typical coronary sclerosis, (2) chronic interstitial myocarditis. The loss of arterioles due to strangulation by fibrous tissue is especially well marked in the areas indicated.

FIG. 15. The coronary arteries of a case of paroxysmal tachycardia. Note (1) the relative increased vascularity of the left auricle associated with mitral incompetence, (2) the sclerosis of the left coronary artery with nipping of its branches and the 'chipped' appearance. There is diminished vascularity of right ventricle.

PLATE 14, FIG. 16. Septum of heart showing chronic myocarditis. Note (1) the loss of finer vascular elements and (2) the marked sclerosis of the left anterior descending artery and its branches. From a case of paroxysmal tachycardia.

FIG. 17. Septum of a case of almost complete occlusion of the left coronary artery due to atheroma and superimposed thrombosis. (1) Vessel in the adventitia of the pulmonary artery. (2) Advanced sclerosis and calcification. (3) Almost complete obliteration of the lumen. (4) Very close anastomotic network in the septum. (5) Kugel's artery and the calcified aortic valves.

FIG. 18. Right accessory coronary artery and coronary thrombosis. (1) Opening of the accessory vessel. (2) Artery cut at the autopsy. (3) Lower level of the thrombosis. (4) Anastomotic channels.

PLATE 15, FIG. 19. From same case as Fig. 18. Note (1) Opening of the right coronary artery. (2) Opening of the accessory coronary artery. (3) Canalized thrombosis. (4) Attenuated opacity due to incomplete occlusion of the first inch of the left anterior descending vessel followed by (5) Complete occlusion. (6) Trauma at the autopsy.

FIG. 20. Septum of the heart; same as case Figs. 18 and 19. Note (1) The occlusion of the left anterior descending branch. (2) Large septal vessel arising from the commencement of the right coronary—a unique occurrence. (3) Wide anastomotic channels.

FIG. 21. Stenosis of the artery to the *a.-v.* node and bundle is shown (1), but there is no diminution in the vascular network (2) in this area. There is some sclerosis of the main coronary vessels.

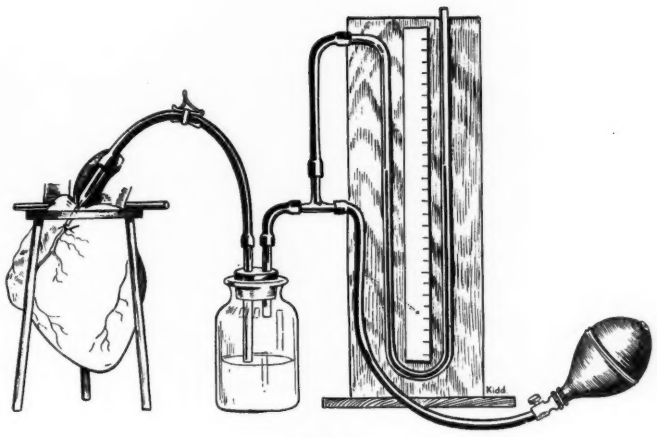

FIG. 1

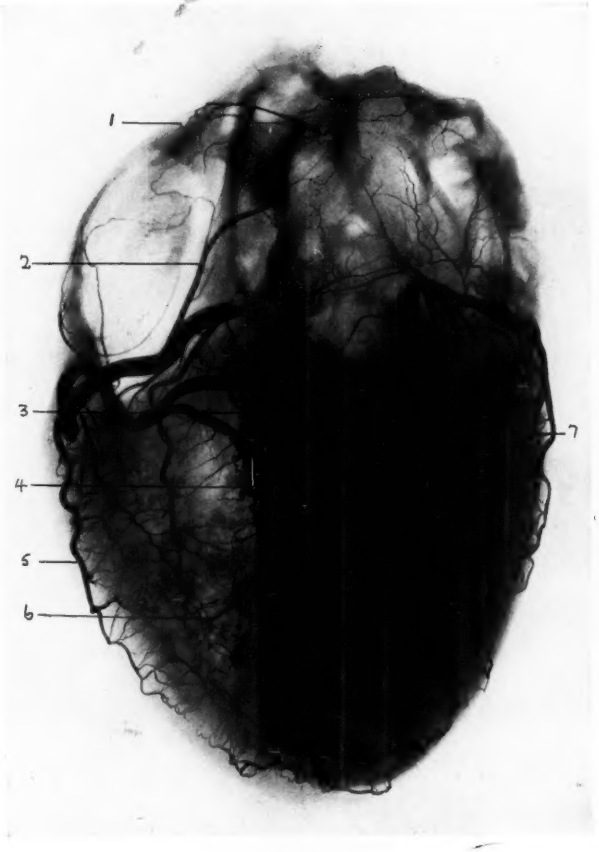

FIG. 2

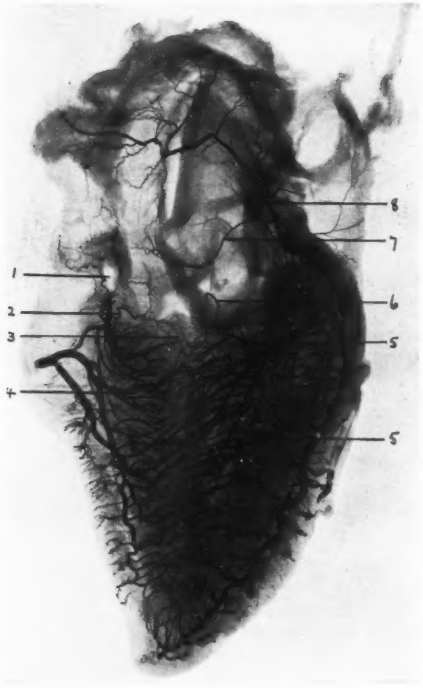

FIG. 3

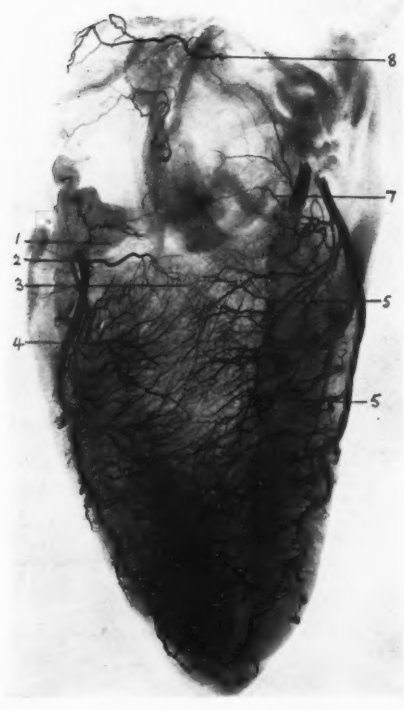

FIG. 4

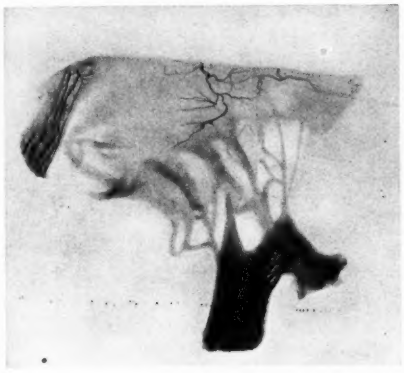

FIG. 6

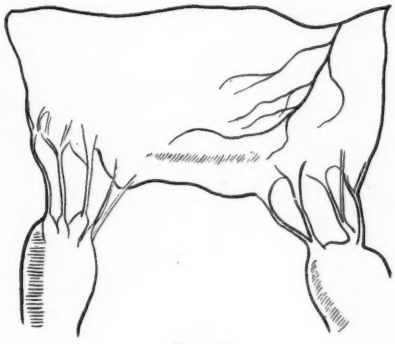

FIG. 7

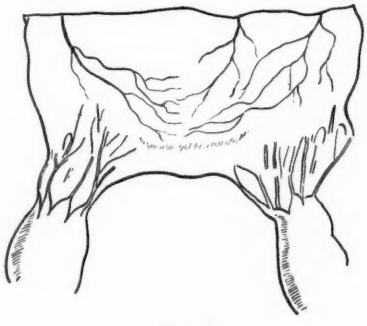

FIG. 5

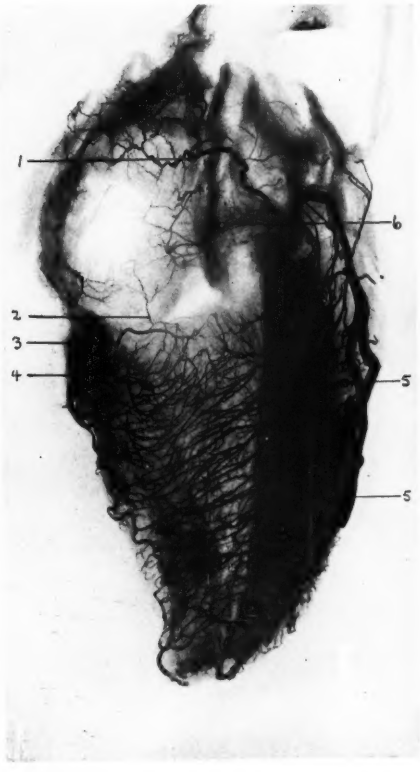

FIG. 8

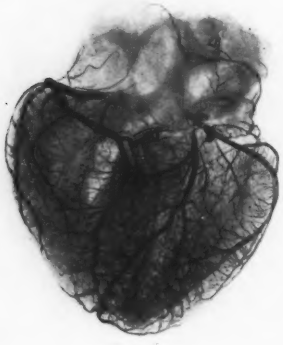

FIG. 9

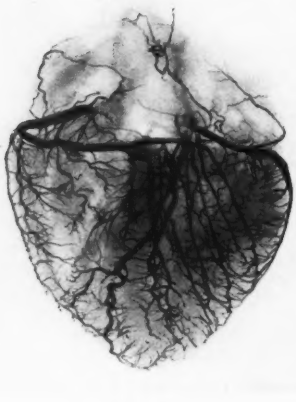

FIG. 9*a*

FIG. 10

FIG. 11

FIG. 12

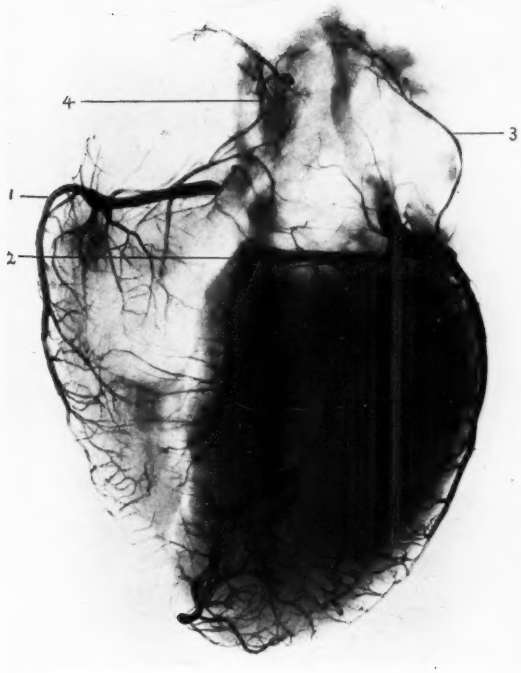

FIG. 13

FIG. 14

FIG. 15

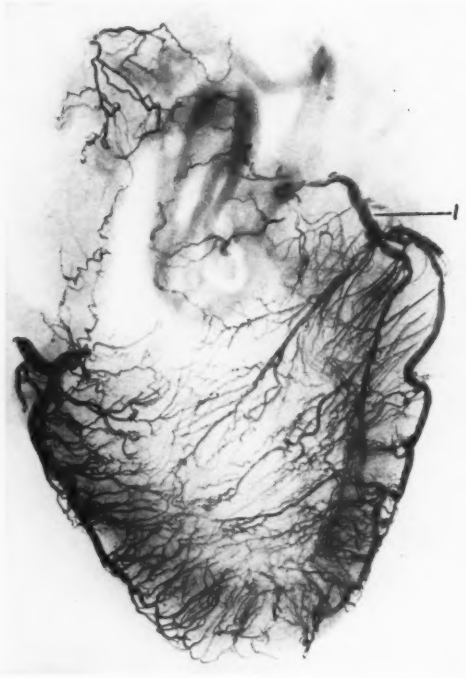

FIG. 16

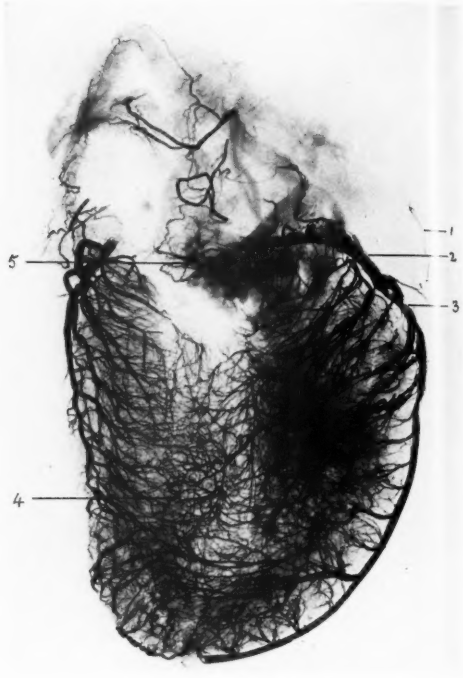

FIG. 17

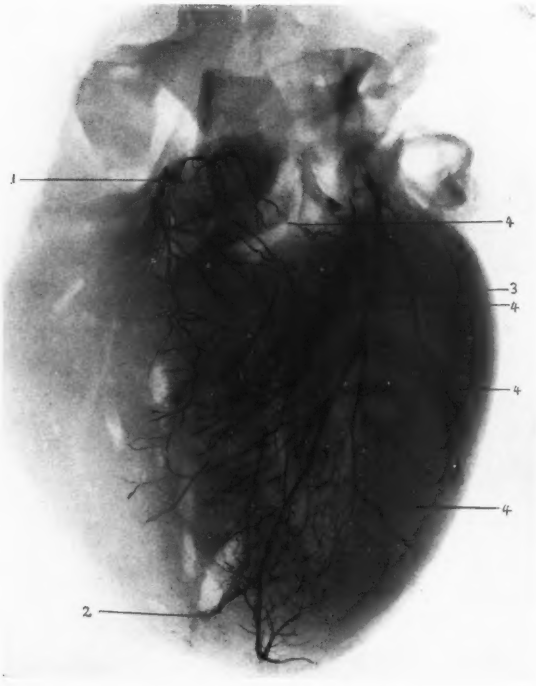

FIG. 18

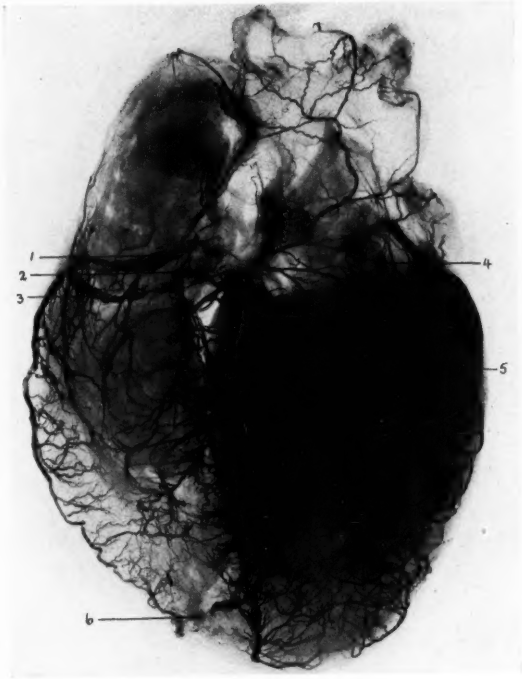

FIG. 19

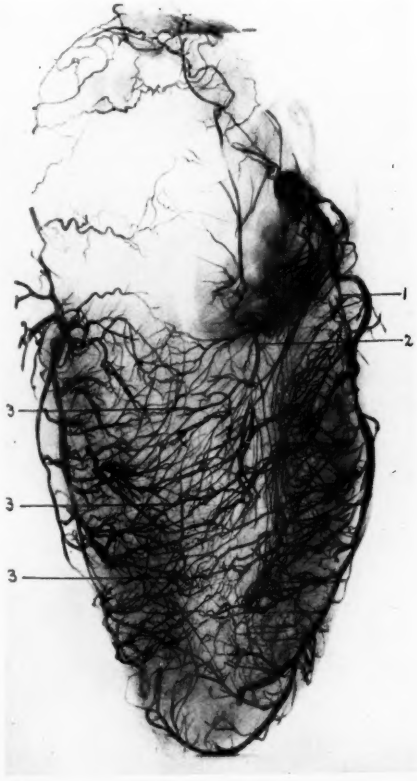

FIG. 20

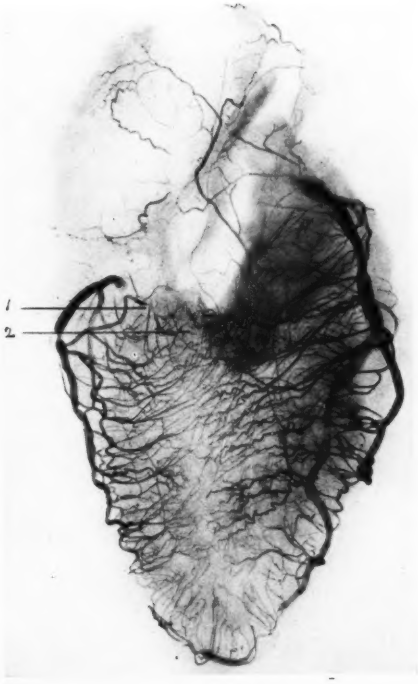

FIG. 21

616.155.1—194.5

THE IMPORTANCE OF FAMILIAL ACHLORHYDRIA IN THE AETIOLOGY OF PERNICIOUS ANAEMIA[1,2]

By JOHN FREDERICK WILKINSON and WILLIAM BROCKBANK

The medical literature of the last fifty years contains occasional references to the familial occurrence of pernicious anaemia. Howard (32) in 1876, who was the first to point this out in a paper on 'Pernicious Progressive Anaemia', described the case of 'a highly respectable married woman aged 46' who suffered from progressive anaemia of a yellow type associated with digestive disturbances and soreness of the mouth. Careful clinical examination failed to detect any local disease. Howard's commentary ran as follows:

'Although satisfied in my own mind that the case was one of pernicious anaemia, yet as the diagnosis lacks the verification of an examination of the blood during life and the body after death, I would not have related it but that the family history appears to me important as proving that a predisposition to anaemia may exhibit itself in families and that it may perhaps be inherited. This patient's youngest sister had been anaemic since childhood; a married cousin had been anaemic since an attack of typhoid fever two years ago; and a grand-uncle died at 62 with symptoms like those manifested by the niece, and was anaemic.'

Since Howard's time several writers, notably Hurst (35), Rolleston (61), and Conner (13), have collected from the published literature records of families in which pernicious anaemia has been present in more than one member; but surprisingly little notice has been taken of what may be an important aetiological factor in the disease. We have, therefore, in addition to our own observations, described later, collected such records as appear to be well attested so as to get a more complete picture of the association of the disease with some hereditary factor. As it is generally agreed that pernicious anaemia is usually associated with achlorhydria,[3] we have included in our investigation into the

[1] Received October 4, 1930.

[2] From the Laboratory for Clinical Investigations and Research, Manchester Royal Infirmary.

[3] The word 'achlorhydria' is employed, although in our experience 'achylia' is frequently more correct. Many observers have not reported on the peptic activity of the gastric contents, and we have therefore no knowledge whether or not the cases they describe have true achylia. The position is complicated by the indiscriminate employment of the two words in the literature. It is of course true that all cases of achylia have *ipso facto* achlorhydria. The term 'achlorhydria' is therefore used here to indicate the absence of free hydrochloric acid in the gastric contents, and 'achylia' to indicate the superadded deficiency of enzymes acting in an acid medium.

familial incidence of the disease the occurrence of familial achlorhydria, as well as those families in which pernicious anaemia and achlorhydria are known to occur simultaneously. Not uncommonly, relatives of patients suffering from pernicious anaemia have achlorhydria although they are either perfectly well or are suffering from an anaemia of a secondary type of which Witts (79) has recently given a full description, under the title of simple achlorhydric anaemia, based on 50 cases.

The families can most conveniently be considered in three groups: (1) Those in which two or more members have pernicious anaemia with or without subacute combined degeneration of the cord (S.C.D.). (2) Those in which pernicious anaemia and achlorhydria exist simultaneously. (3) Those in which achlorhydria is found without pernicious anaemia.

In many of our cases digestive disturbances preceded the onset of the anaemia by months and years, and many cases have been recorded, notably by Riley (60) and Bie (6), in which achlorhydria has been found ten to twenty-five years before the onset of the anaemia; we have never found a record of achlorhydria developing during the course of the disease. There is no doubt that the gastric secretory functions play a very important part in the aetiology of the disease, for it appears to be an almost invariable rule that cases of pernicious anaemia show, or have shown, for many years some deficiency in the gastric secretion. Whether this deficiency is confined purely to the absence of hydrochloric acid and pepsin or includes also some other as yet unknown substance or substances remains to be seen. The evidence, however, that has accumulated from the recent work of Castle (12) and one of us (J. F. W, 74) suggests that there may also be a deficiency of an essential 'anti-anaemic' substance. The difficulties attending satisfactory estimations of the enzymic activities of the gastric fluids and the ease with which hydrochloric acid can be determined explains the comparative rarity with which other than the latter titres have been made.

It may reasonably be stated that pernicious anaemia is constantly associated with a deficient gastric secretion, and as a rule this implies achlorhydria and an absence of peptic activity (so-called 'achylia'). In a few established cases free hydrochloric acid was present, but in subnormal amounts; we have seen five such. The further recent evidence also makes it probable that this deficiency includes an, at present, unknown 'anti-anaemic' substance which has been shown to be present in many animal tissues.

1. *Familial Pernicious Anaemia.*

We have been able to find in the literature records of no fewer than 127 families in which more than one member has suffered from pernicious anaemia. By far the greater number of families recorded show cases in one or two generations only. This is not surprising when it is realized that the disease has only been generally recognized for the last fifty years. There is recorded

one family in which four generations, and six families in which three generations have been affected, and to these we are able to add three from our own cases. We have collected records of twenty-eight families in which the disease occurred in brothers and sisters (one generation only) (Table I). In this table the inclusion of Franconi's cases calls for some comment.

TABLE I. *Recorded cases of pernicious anaemia in brothers and sisters (one generation only).*

	Reference.	Number of Persons Affected.	Relationship.
Andrée	2	2	Patient and sister
Cabot	8	2	Sisters
Cabot	8	2	Brother and sister
Carey	10	2	Sister of patient
Carey	10	2	Brother of patient
Carey	10	2	Brother of patient
Carey	10	2	Sister of patient
Carey	10	2	Sister of patient
Curschmann	14	2	Brothers
Franconi	21	3	Brothers (see p. 221)
Frank	22	2	Sisters
Gilbert and Weil	23	2	Brothers
Houston	31	3	Sisters
Houston	31	2	Brothers
Hurst	36	4	Sister and 3 brothers
Hurst	38	3	2 brothers and a sister
Johannessohn	39	2	Brothers
Kinnicutt	41	3	Not stated
Klein	42	3	Sister and 2 brothers
Morris and Falconer	52	3	Brother and 2 sisters
Morris and Falconer	52	2	Sisters
Roth	62	2	Brothers
Schauman	63	2	Not stated
Schauman	63	2	Not stated
Schüpbach	66	2	Sisters
Tscherning	68	3	Sister and 2 brothers
Ungley and Suzman	71	2	Sisters (one S.C.D.)
Zadek	80	2	Sisters

He has described three brothers between the ages of 5 and 7 years who rapidly died of typical pernicious anaemia. Each boy suffered from microcephaly and had a brown pigmentation of the skin and a purpuric eruption. Necropsies revealed an increase in the lymphoid tissues, fatty degeneration, an abnormal amount of iron in the organs and changes in the bone marrow. An aunt, an uncle, and a grandmother, all on the mother's side, suffered from a haemorrhagic diathesis.

The age of the children introduces some uncertainty about the diagnosis, but the evidence in Franconi's cases justifies the inclusion of that family in this series.

We have also collected twenty-eight families in which the disease affected parent and children (two generations) (Table II), and thirty-one families in which the relationship of the cases was somewhat more complicated (Table III).

The family mentioned by Faber and Gram, and included in Table II, has been recorded on several occasions. In 1924 (20) it consisted of a father

(first generation) and son, who had died of the disease, and a daughter who had achylia together with a simple anaemia. By 1929 (26) Gram had investigated five of the six members of the second generation and had found the disease to be present in three, two males (one recorded in 1924) and a female (the case of achylia and simple anaemia of the original article). Another sister was found to have achylia with simple anaemia. One sister was normal. There were sixteen children in the third generation, and of these Gram was able to examine ten. Their ages ranged from 9 to 22, and they were therefore below the pernicious anaemia age. In no case was achylia or even hypochlorhydria found. Indeed, the majority were found to have hyperacidity. Blood-examinations showed normal blood-pictures in all but one (a case of mild simple anaemia).

TABLE II. *Recorded cases of pernicious anaemia occurring in parent and children (two generations).*

	Reference.	Number of Persons Affected.	Relationship.
Bartlett	3	4	Father and 3 sons
Caccini	9	3	Father, son, and daughter
Carey	10	4	Mother, brother, and sister of patient
Carey	10	3	Mother and sister of patient
Carey	10	2	Father and child
Carey	10	2	Mother and child
Carr	11	2	Mother and son
Faber and Gram	20	4	Father, 2 sons, and daughter
Gram	26		(see p. 221)
Gulland	27	2	Father and child
Gulland	27	2	Father and child
Gulland	27	2	Father and child
Heudorfer	30	2	Father and son
Houston	31	4	Father, son, and 2 daughters
Hurst	36	2	Father and son
Hurst	36	2	Father and son
Hurst	36	2	Father and daughter
Hurst	36	2	Mother and daughter
Hurst	36	2	Mother and daughter (S.C.D.)
Liepelt	44	2	Father and son (both S.C.D.)
Meulengracht	50	2	Father and daughter
Morris and Falconer	52	2	Mother and child
Pentscheff	57	2	Mother and daughter
Schauman	63	2	Mother and daughter
Schauman	63	2	Mother and daughter
Schauman	63	2	Father and son
Schneider and Carey	64	2	Father and son (another child has achlorhydria)
Schroll	65	2	Mother and daughter
Todd	67	2	Father and son (2 grandsons have hypochlorhydria)

Some of the families included in Table III are sufficiently interesting to warrant more detailed descriptions. To facilitate this we have quoted from the original papers.

Bramwell (7) described his family in the following words: 'So far as I know, a hereditary tendency to pernicious anaemia can very rarely be traced; indeed the only instance with which I am acquainted in which the disease appeared to be inherited occurred in the practice of Dr. Allison of Kettering. The patient, a man aged 53, was under Dr. Allison's care with all the typical symptoms of pernicious anaemia and died from the disease. Dr. Allison writes

me: "I venture to think that in this case there is a distinct hereditary taint. His mother died here, aged 60, certified cardiac weakness and chronic diarrhoea; before she died she consulted Dr. Francis, one of the physicians to the Northampton Infirmary, who said that she had a peculiar disease of the blood which would probably be fatal. One aunt died at Mansfield in 1879, aged 55; the certificate gave the cause of death anaemia. Another aunt died at Croydon, aged 46, of morbus cordis. An uncle died at Kettering in 1885, aged 51,

TABLE III. *Familial pernicious anaemia—miscellaneous relationships.*

	Reference.	Number of Generations Affected.	Number of Persons Affected.	Relationship.
Bramwell	7	2	—	(See p. 222)
Carey	10	2	2	Patient and aunt
Decastello	16	2	4	3 sisters and an uncle
Dorst	17	2	5	(See p. 224)
Faber	19	2	4	3 brothers and a nephew
Gilford	25	1	3	Woman and 2 first cousins
Gilford	24, 25	2	4	2 brothers, a sister, and an uncle
Gulland and Goodall	28	2	5	Patient's brother, sister, father, and paternal uncle
Gulland and Goodall	28	2	4	Patient's sister, father, and paternal uncle
Howard	32	2	2	(See p. 219)
Hurst	36	2	2	Man (S.C.D.) and his grandfather.
Hurst	36	2	3	(See p. 224)
Hurst	36	3	5	(See p. 224)
Hurst	36	3	6	(See p. 224)
Liepelt	44	3	3	Man (S.C.D.), his father (S.C.D.), and grandfather
McAdoo	45	4	10	Father, 2 daughters, 2 sons, 3 grandsons, and 2 great-grandsons
Maclachlan and Kline	46	2	13	(See p. 225)
Meulengracht	50	2	3	(See p. 226)
Meulengracht	50	2	5	4 brothers and a nephew
Minot	51	2	6	Brother, 2 sisters, maternal aunt, uncle, and cousin.
Mustelin	53	3	3	Grandmother, mother, and daughter.
Mustelin	53	2	3	(See p. 226)
Panton, Maitland-Jones, and Riddoch	55	2	4	Brother, 2 sisters, and a nephew
Patek	56	2	5	(See p. 226)
Schauman	63	—	3	Two women and their cousin
Schauman	63	—	3	Two women and their cousin
Todd	67	3	4	(See p. 226)
Tscherning	69	1	3	(See p. 227)
Ungley and Suzman	71	2	5	(See p. 227)
Willson	78	2	2	Woman (S.C.D.) and her aunt: another aunt died of grave anaemia and tabes
Witts	79	2	4	2 sisters (1 S.C.D.) and two aunts

certificate, congestion of the liver; his widow tells me that he suffered a good deal from vomiting and feverish attacks during the last year of his life and that he looked exactly like his nephew is at present (typical and advanced pernicious anaemia). An uncle died this year (February) at Wakefield, aged 74; the cause of death was certified by Dr. Eddison of Leeds as pernicious anaemia. The patient has a brother, aged 51, at Willesden very ill just now, like himself in symptoms, I am told".'

Dorst (17) reported his family as follows: 'On August 21, 1924, a woman, aged 44 years, presented herself at the Cleveland Clinic for a general physical examination. The case proved to be one of well-advanced pernicious anaemia with predominant cord changes. Upon taking the family history, we learned that her mother, a sister and a brother had all died of the same disease. Another brother [4] was ill at the time, and she had been on her way to visit him, suspecting that he might have pernicious anaemia, but totally unaware that she herself was a victim of the disease. When we investigated the brother's case, we learned that her suspicion was well founded, for he had the same disease. Here we had a remarkable group of cases, consisting of five members of a single immediate family who had either died from the disease, or were in its late

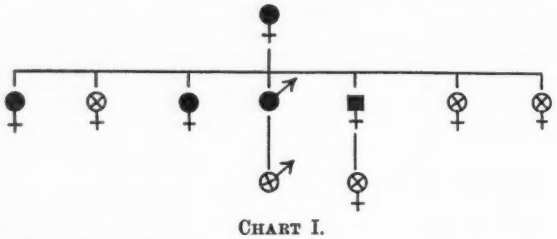

CHART I.

In this and the other charts

● = Pernicious anaemia.

■ = The pernicious-anaemia-subacute-combined-degeneration-of-the-cord syndrome.

⊗ = Achlorhydria without pernicious anaemia.

A = Simple anaemia.

The figures indicate the number of other members of the family.

stages. In three of these cases we had been fortunate enough to obtain direct and conclusive evidence which has substantiated the diagnosis. In the case of the mother and one daughter it was too late to obtain direct evidence, but the histories and indirect evidence are so conclusive that there can be little doubt as to the accuracy of the diagnosis. It was possible for us to examine six other members of this family group for the signs of Addison's anaemia, and especially for alteration in the gastric secretions. In each case the fractional gastric analysis was made. Only two had a normal secretion; two had complete achlorhydria and two had very marked hypochlorhydria closely approaching an achlorhydria. None of these latter cases which ranged in age from 19 to 54 years showed an abnormal blood-picture. We know that those members of the family that died from the disease had an achlorhydria, therefore in a group of eleven individuals in one family we find that nine had lack of acid in the gastric secretions, and five of these developed pernicious anaemia.' (Chart I.)

Hurst described three interesting families as follows: (i) 'The most remarkable case was that of a woman with Addison's anaemia, whose parents were first cousins, her father's father and mother's father being brothers. Her father and her mother's sister had both died of Addison's anaemia; unless this is a coincidence they must have inherited the predisposition from either the grandfather or grandmother they had in common' (36). (Chart II *a*.) (ii) 'The brother, father, paternal uncle, and paternal grandfather of a case of subacute combined degeneration of the spinal cord had all died of Addison's anaemia' (36). (Chart II *b*.) (iii) A woman of 50 years, in good health, but suffering from slight diarrhoea, sought medical advice as she was alarmed because several

[4] It will be observed that there are discrepancies in this account and the accompanying chart, but we have quoted verbatim from the original paper.

members of both sides of her family had all died of pernicious anaemia. Her sister, her mother, her paternal grandmother, and a cousin of her father had all died from pernicious anaemia, and a paternal first cousin also had it. She herself had megalocytosis, glossitis, and absolute achlorhydria (36). (Chart II *c*.)

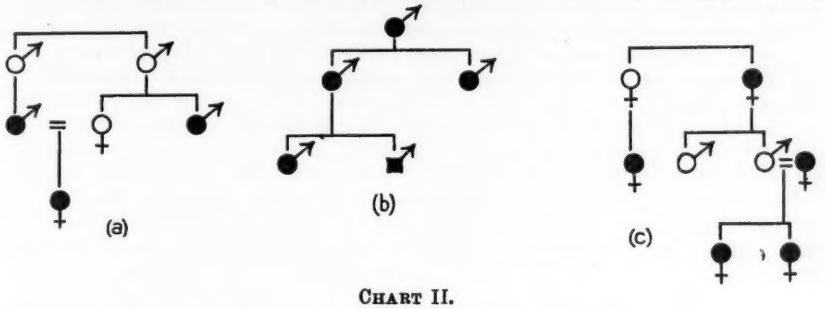

CHART II.

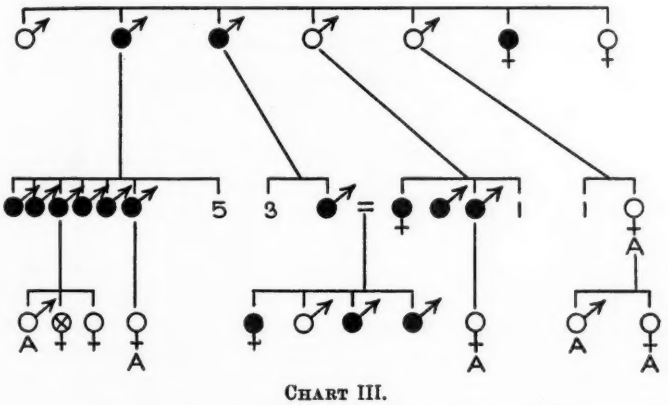

CHART III.

The family described by Maclachan and Kline (46) is perhaps the most remarkable of all as it extends over four generations. In the first generation the parent died at the age of 44 of an anaemia characterized by a deathly pallor. The second generation consisted of five brothers and two sisters; of these two brothers and a sister died with a peculiar yellow anaemia. The third generation consisted of the children of four of the sons, who incidentally had married four sisters; the second son (second generation) who died of the anaemia, had eleven children, six of whom developed pernicious anaemia (one having changes in the spinal cord). The third son (second generation), who had also died of anaemia, had four children, one of whom died of pernicious anaemia. The fourth son (second generation) had four children, three of whom were affected, and the fifth son (second generation) had two, who were both unaffected although one had a secondary anaemia. In the fourth generation there were several cases of secondary anaemia, and one case of hypochlorhydria; but by far the most interesting group was the family of four children whose parents were first cousins and who had both died of pernicious anaemia. Of this family three developed pernicious anaemia, but it was impossible to trace the whereabouts of the fourth, and unfortunately nothing was known of his condition. Details of blood examinations of six of these patients are given in the paper, and it is curious that, with one exception, nucleated red cells were never found. (Chart III.)

Meulengracht (50) described his cases as follows: 'In the family in question two brothers had died from pernicious anaemia. Immediately after the death of one of these the son was examined by me. He looked and felt perfectly healthy, without a trace of anaemia, but examination showed the following: haemoglobin, 98 per cent.; erythrocytes, 3,900,000 per c.mm.; colour index, 1·25. Films showed a typical megalocytic picture, and the average diameter of the corpuscles was increased to 8·8 μ. There was a leukopenia, bilirubinemia, and urobilinuria, a slight platelet deficiency, a gastric achylia, and the characteristic periodic glossitis. In spite of the 98 per cent. haemoglobin the patient had a classical pernicious anaemia, which was fully confirmed by subsequent events. This patient was discovered in the well-known initial stage of the disease, but except for a painstaking examination would have been classified as healthy. A further investigation of this family shows the interesting fact that not less than six individuals beside the three cases of frank pernicious anaemia had suffered from gastric achylia. Of these six, four also had the typical glossitis.' (Chart IV.)

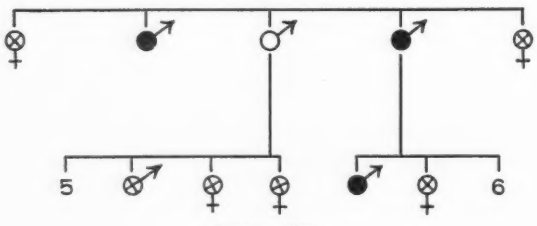

CHART IV.

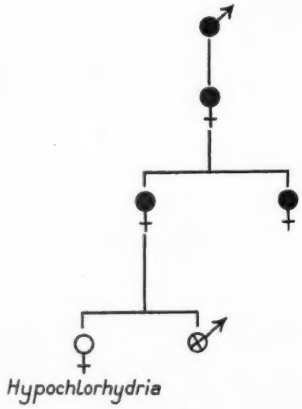

CHART V.

Mustelin's cases (53) are of interest if only for the manner in which they have repeatedly been misquoted. He described a family in which a woman, her mother's sister, and a female cousin, suffered from pernicious anaemia. Two of her children had colour indices of 1·14 with normal gastric secretion. In addition, a sister of the patient had anaemia of a secondary type together with 'achylia'.

Patek (56) recorded 'three fatal cases of primary anaemia (two brothers and a sister) and two of secondary anaemia (two sisters) in members of one family; primary anaemia in a paternal cousin, and a fifth case of fatal primary anaemia in a paternal uncle'. The examination of the blood removes any doubt that these patients suffered from pernicious anaemia although one of the brothers had the aplastic form.

Of Schauman's cases we have quoted those only that seemed to be ordinary pernicious anaemia as opposed to bothriocephalus anaemia, of which he described a further fifteen families.

Todd (67) described a family as follows: 'In one of my cases of pernicious anaemia there was a strong family history—the patient's mother and grandfather had died of the disease. Having diagnosed Addison's anaemia I advised that the relatives should be examined; I found that both her children were anaemic, and that one had complete achlorhydria, and also that one of the patient's sisters was in the early stages of the disease.' (Chart V.)

From a genealogical point of view Tscherning's family (69) is particularly interesting. Three sisters were concerned; their father married twice, the second time to a sister of his first wife. The first wife died of cancer of the stomach. She had four children, of whom one daughter died of anaemia at the age of 12 and another daughter died of pernicious anaemia. The second wife had five children. One daughter was weak and easily tired but refused to be examined. The second and third daughters developed pernicious anaemia. The son was an epileptic idiot. (Chart VI.)

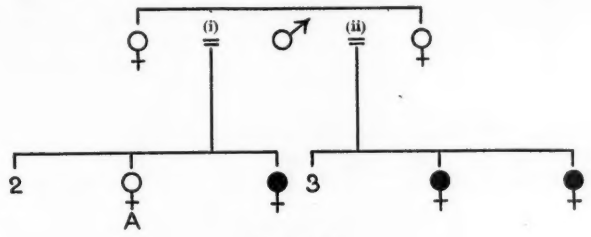

CHART VI.

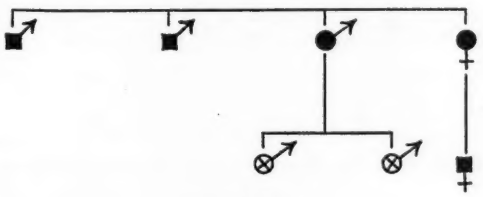

CHART VII.

Ungley and Suzman (71) reported cases of pernicious anaemia and subacute combined degeneration of the cord co-existing in the same family. Two generations were involved, and in the second generation the disease occurred at the early age of 29, and was rapidly fatal. The family consisted of a sister and three brothers and the daughter of the sister. Three of them had subacute-combined degeneration of the cord and the other two pernicious anaemia. In addition, two of the four sons of one of the brothers had achlorhydria. (Chart VII.)

Besides these families the following observers have quoted 40 families without giving genealogical details: Hurst (38), one family in addition to the ten already quoted; Levine and Ladd (43), 9 families; Dorst (17), 3 families: Schauman (63), a further 9 families, making 16 in all; Riley (59), 12 families; Charles Hunter (33) and Zadek (80), 3 families each; whilst Davidson and Gulland (15) have 'frequently obtained the history of one other case in a family'. Curschmann (14) has seen more than one example and Matthes (49) has several times seen the familial occurrence of pernicious anaemia; on one occasion there were three instances in the same family.

We have observed fourteen patients, one or more of whose relatives were said to have suffered from pernicious anaemia. In each case the diagnosis was reasonably certain, but in only four families could detailed examinations of the relatives be made. In these fourteen cases the relations affected were

(1) a brother, (2) mother and brother, (3) father and brother, (4) sister, (5) father, (6) father and grandfather, (7) aunt, (8) father and paternal grandfather, (9) aunt—a daughter was found to have hypochlorhydria (Table VII, K), (10) daughter probably (Table VII, V 2), another daughter has achlorhydria, (11) brother, (12) daughter (Table VII, Q 1), (13) brother.

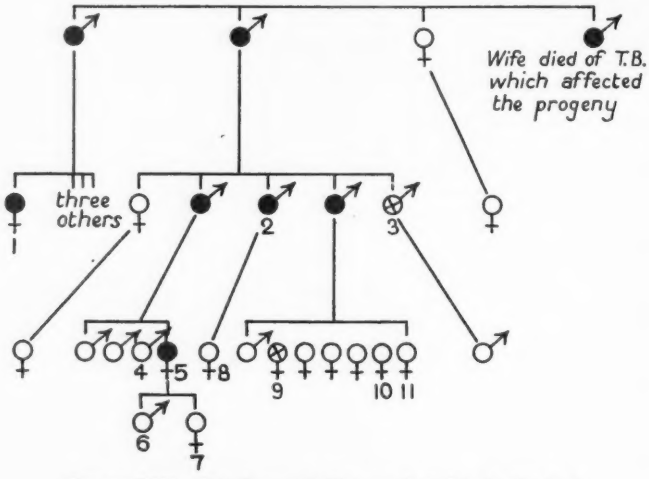

CHART VIII. The figures 1-11 are referred to in the text.

Family number 14 covers four generations (Chart VIII). The first generation consisted of three brothers, all of whom died of anaemia, and a sister, who was apparently unaffected. All three brothers had a yellowish appearance and closely resembled the members of the second generation when they had typical and advanced pernicious anaemia. The second generation consisted of the children of all four members of the first generation. The eldest son had four children—a son died of rheumatism, a daughter of Bright's disease, and another daughter at the age of 70 from heart failure and 'an abdominal tumour'. The third daughter aged 60 is alive and suffering from pernicious anaemia (Case 1), (Table IV). The second son (first generation) had five children—a daughter who suffered from anaemia and who died after pregnancy at the age of 44 (her only child died at the age of two months). Two sons died of pernicious anaemia and a third is affected and is now on the liver diet (Case 2). The fourth son is alive and well although he has achlorhydria (Case 3). The third son (first generation) married a wife who died from tuberculosis at an early age. Their family of five we have been unable to examine although we understand that several of the children died from pulmonary tuberculosis. The fourth member of the first generation, the daughter, had a daughter now aged 50 and apparently healthy. The third generation consists of the children of the four brothers (second generation), three of whom had pernicious anaemia and the fourth achlorhydria. The eldest had four children—a son killed in the war—another son, aged 34, who is alive but not strong—another son aged 19 and apparently healthy (Case 4), and a daughter aged 37 (Case 5) found to have had achylia on two separate occasions at an interval of six months. During this period, although the patient was taking hydrochloric acid and pepsin (77), the blood picture changed from one of apparent normality to one strongly suggestive of pernicious anaemia (see Table IV).

The latter's two children, aged 10 and 12 years (Cases 6 and 7), are healthy with normal blood counts. The second son has one healthy daughter, aged 30 (Case 8), apparently not affected. The third son had a son and six daughters—we have been able to examine three of these (Cases 9, 10, and 11)—and one daughter aged 30 has achlorhydria. The fourth son, who has achlorhydria, has an apparently healthy son aged 18 years. The family thus contains seven (possibly eight) cases of pernicious anaemia and three of achlorhydria with normal blood picture. The details of our examinations are given in Table IV.

TABLE IV.

Case No.	Age.	Sex.	Main Symptoms.	R.B.C.'s in Millions.	Hb. %	Colour Index.	Megalocytosis	Nucleated R.B.C.'s.	Platelets.	Fractional Gastric Analysis. Peptic Activity.	Fractional Gastric Analysis. Acidity.
1	62	F	Anaemia, dyspepsia, glossitis, &c. (on liver diet)	4·55	84	0·92	present	—	fair	nil	achlorhydria
2	56	M	Anaemia, dyspnoea	0·890	26	1·6	marked	present	scanty	nil	achlorhydria
3	47	M	Dyspepsia	5·900	108	0·92	—	—	abundant	nil	achlorhydria
4	19	M	None	5·560	100	0·9	—	—	abundant	—	—
5	37	F	Dyspepsia,	5·300	80	0·73	—	—	abundant	nil	achlorhydria
			6 months later	3·480	70	1·02	—	—	abundant	—	—
6	12	M	None	4·450	88	1·0	slight	—	abundant	—	—
7	10	F	None	5·575	92	0·84	—	—	abundant	—	—
8	30	F	None	4·475	92	1·0	—	—	abundant	normal	normal
9	26	F	None	4·467	70	0·79	—	—	abundant	nil	achlorhydria
10	12	F	None	4·650	90	0·97	—	—	abundant	—	—
11	twin of Case 10	F	None	5·150	100	0·97	—	—	abundant	—	—

There can be little doubt that familial pernicious anaemia is much more frequent than is generally supposed. Owing to its character, the condition is not infrequently diagnosed as cancer, hepatic disorder, anaemia, or some neurological lesion, and we have frequently been told that blood relations of our patients have died from these diseases. It is, therefore, probable that the number of recorded cases of familial pernicious anaemia is very much less than the actual number.

It will be noticed that, whereas the bulk of cases are limited to near relatives (e.g. parent and child or brother and sister) there are a number of families where uncles and aunts and cousins have been affected.

The evidence is undoubtedly in favour of a hereditary factor as opposed to transmission by direct infection. Our series does not contain a single case occurring in any one living or associated with, but not related to, a case of pernicious anaemia.

It will be observed that we have not been able to trace more than one example of husband and wife who were both affected (Maclachlan and Kline): in this case they were first cousins and the disease was prevalent in the previous generation. Conner examined sixty marital partners with similar results. The real cause, therefore, must be looked for in endogenous factors, for the greater the distribution of the disease throughout the family and the greater the number of families recorded, the more probable is it that hereditary or familial predisposition plays an important part in the aetiology of the disease.

II. *The Simultaneous Occurrence of Pernicious Anaemia and Achlorhydria in Families.*

From the aetiological point of view these families are the most interesting of the series. As achlorhydria precedes the onset of the anaemia, in some cases by many years, it may be assumed that not a few of the cases recorded in this group as suffering from achlorhydria without pernicious anaemia ultimately developed, or will develop, the disease in the way we have recorded (Case 4). It is probable that achlorhydria indicates that the gastric secretory deficiency may be the endogenous cause of the pernicious anaemia referred to earlier.

Weinberg (72) showed that this achlorhydria occurs at an early age; he examined the gastric contents of twenty-two children of twelve patients suffering from pernicious anaemia and found that nine of them had 'achylia'. Perhaps the most interesting case was that of a man with pernicious anaemia who had four children, of whom three, a boy of 10, a boy of 6, and a girl of 4 years, had 'achylia', suggesting that in these children the deficient gastric secretion was hereditary.

If pernicious anaemia is sometimes difficult to diagnose, then achlorhydria is far harder. It is true that some symptoms, such as diarrhoea and flatulent dyspepsia, suggest the impairment of secretion in the stomach, but it is also true that many persons with achlorhydria are symptomless, and that the bulk of the cases of familial achlorhydria recorded have been found by a systematic examination of the relatives of cases of pernicious anaemia no matter how well they were. It must be obvious that very many persons with achlorhydria are never diagnosed correctly and, therefore, the question of simultaneous familial pernicious anaemia and achlorhydria is much more common and consequently more important than is generally supposed.

We have been able to collect from the literature fifty-two families showing simultaneous pernicious anaemia and achlorhydria (Table V), and of these nine have already been recorded in the first section of this communication. In addition to these figures Conner (13) found achlorhydria in 40 out of 154 relatives of 109 cases of pernicious anaemia. As he does not give the genealogical details we are not aware of the number of families involved.

Zadek's (80) results call for a word of comment. He examined forty-six relatives of twenty cases of pernicious anaemia. The relations were mostly

brothers and sisters or children. One relative of each of three cases of pernicious anaemia had complete achylia gastrica with absence of pepsin. Seven had achlorhydria; fifteen, diminished acidity; six, hyperchlorhydria, and fifteen had normal gastric juice. Very seldom did two relations of a particular

TABLE V. *Recorded cases of pernicious anaemia and achlorhydria occurring simultaneously in the same family.*

	Reference.	Relationship to Patient suffering from Pernicious Anaemia.
Berglund	5	Daughter
Dorst	17	See Table III
Evans	18	Sister
Faber and Gram	20	See Table II
Harris	29	Daughter
Hurst	36	Sister
Hurst	36	2 daughters
Hurst	34	Daughter
Hurst	36	Brother
Hurst	36	Sister
Hurst	38	4 other families—relationship not stated, making 9 families in all
Maclachlan and Kline	46	See Table III
Martius	48	3 children
Martius	48	Son
Martius	48	Daughter (another daughter had hypochlorhydria)
Meulengracht	50	See Table III
Mustelin	53	See Table III
Neuburger	54	Son
Queckenstedt	58	3 children
Queckenstedt	58	Child (3 others had hypochlorhydria)
Schneider and Carey	64	Child
Schneider and Carey	64	Child
Schneider and Carey	64	Child
Schneider and Carey	64	See Table II
Schneider and Carey	64	2 sisters
Todd (family D)	67	Daughter
Todd („ E)	67	Son
Todd („ B)	67	Daughter
Todd („ B 1)	67	See Table II
Todd („ W)	67	See Table III
Ungley and Suzman	71	See Table III
Weinberg	72	Son and daughter
Weinberg	72	Sister
Weinberg	72	3 Children
Weinberg (4 cases)	72	Child
Witts	79	Child
Zadek (10 cases)	80	(See p. 230)

case give results at all similar. Blood examinations were made in all cases, but there was never a suggestion of a pernicious anaemia blood picture. This statement is in striking contrast to the opinion of Weinberg (73), who advises that a blood examination should be made in all cases of achylia gastrica; he observed that many of these cases show signs of early pernicious anaemia, such as slight megalocytosis, scanty platelets, and a colour index of at least one.

Four observers have published figures showing the percentage occurrence of achlorhydria in the relatives of cases of pernicious anaemia. As these vary strikingly the results are shown in Table VI.

TABLE VI.

	Reference.	Number of Relations Examined.	Number found to have Achlorhydria.	%
Conner	13	154	40	26·0
Neuburger	54	29	1	3·4
Weinberg	72	24	10	41·7
Zadek	80	46	10	21·7

In a series of 160 cases of pernicious anaemia we have examined fifty-two relatives of twenty-six of these cases. Eleven of these relatives of one case have already been detailed (Table IV); of the remainder (Table VII) and the eight cases of family F, who were not suffering from pernicious anaemia (Table IV, 3, 4, and 6 to 11), it will be observed that forty-four had full blood counts and forty fractional gastric analysis. Two (Q. and V. II) of these cases are regarded as suffering from pernicious anaemia and therefore are not considered in the following analyses. The average erythrocyte count in these cases was relatively high, being 5·330 millions per cubic millimeter in the males (maximum 5·968, minimum 4·140) and 4·880 in the females (maximum 5·950, minimum 4·096); the average haemoglobin value was: males 100 per cent. (maximum 112 per cent., minimum 44 per cent.), females, 91 per cent. (maximum 104 per cent., minimum 66 per cent). It is noteworthy that only one male had a haemoglobin value of less than 100 per cent., and that he was suffering from pyloric stenosis. The platelets were invariably abundant, and irregularity in the size of the erythrocytes was observed in fifteen cases. Fifteen relations showed a colour index equal to or greater than unity.

The results of fractional analyses on thirty-eight relatives may be grouped together conveniently as follows: (1) *Achylia gastrica* (no free acid or pepsin), four cases. (Two in Table VII, two in Table IV.) (2) *Achlorhydria* (with reduced peptic activity), five cases. (3) *Hypoacidity* (maximum titre obtained for free hydrochloric acid less than twenty units). (*a*) Normal peptic activity, 7; (*b*) diminished peptic activity, 9; total, 16 cases. (4) *Normal acidity* (20–60 units free acidity), twelve cases. (5) *Hyperacidity* (greater than 60 units), one case.

It will thus be seen that nine (23·7 per cent.) showed achlorhydria and sixteen (42·1 per cent.) hypochlorhydria, making a total of twenty-five cases (65·8 per cent.) of the relatives examined with a gastric secretory deficiency—a figure in considerable excess of that recorded by Bennett and Ryle (4) in healthy individuals. It should, however, be noted that the peptic activity does not always show a corresponding deficiency. In the nine cases with achlorhydria four were entirely deficient, whereas the remainder showed only a reduced peptic activity. Similarly, in the sixteen cases with hypoacidity, only nine gave a corresponding reduction in the pepsin values. This is in marked contrast to the results obtained with cases of pernicious anaemia, in which there is usually a complete absence of hydrochloric acid and pepsin (Wilkinson and Brockbank (76)).

III. *Familial Achlorhydria not associated with Pernicious Anaemia or Subacute Combined Degeneration of the Cord.*

This group of cases is by far the smallest of the three since but little opportunity is afforded of examining members of apparently healthy families for the possible occurrence of familial achlorhydria. We have collected fourteen families from the literature showing achlorhydria in more than one member. In addition several authors state that they have seen examples without giving details. Seven families are described by Albu (1); two by Hurst (37)—a brother and sister and two sisters, one of each pair having been originally examined on account of gastric disturbances; one by Jung (40)—a brother and sister, the latter complaining of dyspepsia, and one by Schneider and Carey (64)—a parent and daughter. Udaondo (70) found achlorhydria in a woman with chronic diarrhoea, and on this account was able to examine her son and daughter, both of whom also had the same complaint associated with achlorhydria. In addition Martinez (47) states that he has seen twenty to thirty cases of achylia in parents and their children, or in two or three other members of their families, but he did not give any further details except in the two following remarkable families.

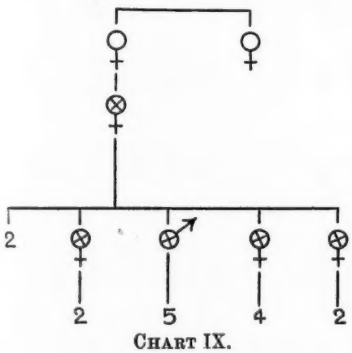

CHART IX.

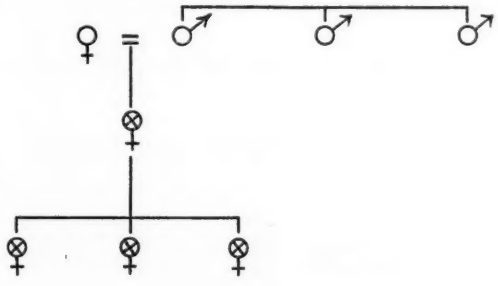

CHART X.

The first (Chart IX) consisted of four generations: two sisters in the first generation had chronic diarrhoea and indigestion and ultimately died of gastric cancer. The daughter of one of these had diarrhoea since youth, associated with achlorhydria and a rapidly emptying stomach—she died of gastric cancer four years after first coming under observation. This woman had six children—two died in infancy whilst the other four (three females and a male) were all troubled with gastro-intestinal disturbances, colic, and chronic diarrhoea, and all had achlorhydria. These four and their mother were all of a very nervous hysterical type. The fourth generation consisted of the thirteen children of the four members of the third generation; five of them had achlorhydria, three without any symptoms.

The second family (Chart X) showed a similar familial tendency to achlorhydria associated with chronic diarrhoea and hysterical neurotic temperaments. It consisted of a female patient and her three daughters representing the second and third generations all with achlorhydria; in the first generation the patient's father died of gastric cancer and his two brothers had gastric disturbances. His wife was a hysterical neurotic woman like her daughter.

TABLE VII.

Family Letter.	Relationship to Case of P. A.	Age.	Symptoms.	R.B.C.'s (in Millions)	Hb. %	Colour Index.	Megalocytosis.	Nucleated R.B.C.'s.	Platelets.	Fractional Gastric Analysis. Peptic Activity.	Acidity.
A. I	Son	22	None	—	—	—	—	—	—	Normal	Normal
II	Daughter	21	None	5·125	86	0·75	—	—	Abundant	Normal	Normal
B.	Daughter	20	Anaemia, dyspepsia	4·790	95	1·1	Slight	—	Abundant	Normal	Hypoacidity
C.	Son	31	Dyspepsia	4·600	102	1·1	—	—	Scanty	Normal	Normal
D. I	Daughter	27	None	5·400	94	0·87	—	—	Abundant	Normal	Hypoacidity
II	Daughter	25	None	5·950	100	0·83	—	—	Abundant	Normal	Hypoacidity
III	Daughter	21	None	5·147	96	0·93	—	—	Abundant	Normal	Hypoacidity
IV	Daughter	12	None	4·120	90	1·09	—	—	Abundant	—	—
E.	Son	31	None	5·968	108	0·9	—	—	Abundant	Normal	Normal
F.	See Table IV.										
G.	Mother	60	Dyspepsia	4·687	90	0·96	Slight	—	Abundant	Diminished	Achlorhydria
H.	Brother	26	Dyspepsia	5·416	102	0·94	Slight	—	Abundant	Normal	Normal
I.	Son	29	Dyspepsia	—	—	—	—	—	—	Diminished	Hypoacidity
J.	Brother	39	Dyspepsia, sore tongue	5·175	110	1·07	—	—	Abundant	Normal	Normal
K.	Daughter	35	None	4·896	92	0·95	—	—	Abundant	Diminished	Hypoacidity
L.	Son	32	None	5·632	112	1·0	—	—	—	Diminished	Normal
M. I	Daughter	31	Dyspepsia, paraesthesia	3·950	88	1·1	Present	—	Abundant	Diminished	Hypoacidity
II	Daughter	27	Grave's disease, colitis	4·875	96	0·98	Slight	—	Abundant	Diminished	Hypoacidity
III	Daughter of M. I	3	None	4·096	90	1·1	—	—	—	—	—

N.	I	Brother	39	Dyspepsia, paraesthesia	5·012	104	1·04	—	—	Abundant	Diminished	Achlorhydria
	II	Son	21	None	5·612	104	0·93	—	—	Abundant	Normal	Hypoacidity
	III	Daughter	18	None	5·250	104	1·0	Slight	—	Abundant	Normal	Hypoacidity
O.		Daughter	36	Dyspepsia	4·896	96	1·0	—	—	Abundant	Diminished	Achlorhydria
P.	I	Daughter	25	None	4·533	94	1·03	—	—	Abundant	Diminished	Hypoacidity
	II	Son	22	None	5·750	102	0·89	Marked	—	Abundant	Normal	Normal
	III	Daughter	18	None	4·950	92	0·93	Slight	—	Abundant	Diminished	Hypoacidity
	IV	Niece	19	None	4·950	92	0·93	—	—	Abundant	Normal	Normal
Q.		Daughter	38	Dyspepsia	4·488	94	1·04	Present	—	Abundant	Nil	Achlorhydria
R	I	Sister	46	Dyspepsia	5·362	92	0·86	—	—	Abundant	Nil	Achlorhydria
	II	Son	22	Dyspepsia	5·475	106	0·96	Slight	—	Abundant	Diminished	Normal
	III	Son	17	Diarrhoea	5·562	100	0·9	Slight	—	Abundant	Diminished	Hypoacidity
S.		Son	14	Easily bruises, Dyspepsia	4·862	100	1·03	—	—	Abundant	Nil	Achlorhydria
T.		Daughter	33	None	4·896	92	0·95	—	—	Abundant	Diminished	Hypoacidity
U.		Mother	48	None	4·800	66	0·68	Slight	—	Abundant	—	—
V.	I	Daughter	32	Dyspepsia	—	—	—	—	—	—	Diminished	Achlorhydria
	II	Daughter	30	Dyspepsia	4·800	95	0·98	Marked	—	Abundant	Diminished	Achlorhydria
	III	Son	27	Dyspepsia	5·860	110	0·94	Present	—	Abundant	Normal	Hyperacidity
W.		Half-sister	—	—	—	—	—	—	—	—	Diminished	Hypoacidity
X.		Daughter	—	None	5·360	99	0·9	—	—	Abundant	Diminished	Achlorhydria
Y.		Brother	45	Pyloric stenosis	4·140	44	0·54	Marked	—	Abundant	Normal	Hypoacidity
Z.		Daughter	25	Haematemesis, haemoptysis	4·360	88	1·0	Marked	—	Abundant	Normal	Normal

One of us (J. F. W.) (75) has observed three families in which achlorhydria or achylia has been present in more than one member. In each case the original patient had complained either of a chronic diarrhoea or one or other of the dermatoses. In one family five members, representing four generations, had been affected with a chronic diarrhoea. Two of these were dead, but the remaining three were examined by fractional gastric analysis and found to have achylia gastrica (Chart XI). There were not any other members of these generations. Hydrochloric acid therapy had relieved the gastro-intestinal conditions up to the present time. In the other two families, achylia gastrica was found in a mother and daughter in each family, one member of each having been examined on account of a chronic skin condition. It will thus be seen that apart from the familial occurrence of achlorhydria in pernicious anaemia and subacute combined degeneration of the cord there is a familial achlorhydria associated with other conditions such as urticaria, chronic diarrhoea, and many gastro-intestinal conditions. Further extension of this work may make this more clearly apparent in a larger series of cases.

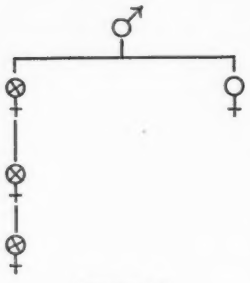

CHART XI.

Summary.

1. We have collected from the literature: (i) 125 families in which two or more members were affected with pernicious anaemia with or without the complication of combined degeneration of the cord; (ii) 51 families in which pernicious anaemia and achlorhydria existed simultaneously; and (iii) 14 families in which achlorhydria was found without pernicious anaemia. Other references are quoted from the literature, but familial details have not always been given.

2. From our own investigations in a series of 160 cases we have been able to add to these groups: (i) 14, (ii) 8, and (iii) 3 families.

3. An example of familial pernicious anaemia is reported in which four generations were involved. Eight members of the family have suffered from pernicious anaemia, and three other members have achylia gastrica with normal blood pictures at the present time.

4. When pernicious anaemia occurs in more than one member of the same household it is always amongst the blood relations, and no case has been recorded in other than such relatives. The main factor in its occurrence must, therefore, be endogenous and neither exogenous nor environmental.

5. Numerous references have been made to the percentage occurrence of achlorhydria in relatives of cases suffering from pernicious anaemia, and figures from 3 per cent. to 42 per cent. have been quoted. Sixty-one out of 253 relatives with pernicious anaemia have been found to have achlorhydria by various authors, and to this figure we have been able to add 9 out of 38 relatives (23·7 per cent) of 26 patients. This gives a total of 70 cases of familial achlorhydria in 291, an average of approximately 24·1 per cent.

6. Almost half of our cases showing achlorhydria also have no peptic activity, i. e. 'achylia gastrica'.

7. In our investigations of relatives of patients suffering from pernicious anaemia we have several times found individuals actually suffering from the disease in its early stages.

8. The blood pictures obtained in an examination of relatives show an average of 5·330 millions erythrocytes per c.m., and 100 per cent. haemoglobin in males and 4·880 and 91 per cent. respectively in females.

9. A much more rarely reported condition of familial achlorhydria unassociated with pernicious anaemia or postero-lateral sclerosis has been considered. The most interesting of our own three cases was a family of four generations with chronic diarrhoea—three generations showing achylia gastrica. Our evidence indicates that there is a definite familial occurrence of achlorhydria usually associated with diminished peptic activity.

10. Considering the series as a whole it is obvious that heredity is a very important factor in the aetiology of pernicious anaemia. It is probable that this factor is a hereditary diminution or predisposition to such in the gastric secretory functions, and evidence is presented from the literature and our own experience in support of this contention.

The work has been done by one of us (W.B.) under the tenure of a Dickinson Scholarship.

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THE CONCEPTION OF 'NEPHROSIS'[1]

OBSERVATIONS ON THREE FATAL CASES

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With an Account of the Histological Changes by S. L. BAKER
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With Plates 16 to 18

I. *Introductory.*

The conception of nephrosis, as understood by the writers, is an attempt to separate from the welter of conditions included under 'nephritis' a distinct group worthy of classification as a separate disease.

Müller (1), who first proposed the use of this word, based his views almost entirely on cases seen at autopsy, and it is only more recent work, chiefly by American observers such as Epstein (2), Murphy and Warfield (3), Clausen (4), and Fishberg (5), and German workers such as Munk (6) and Volhard and Fahr (7), that has evolved a clinical and chemical basis to be added to the morbid anatomy in support of the conception.

It is not, perhaps, superfluous at this point to repeat what are considered to be the essential findings in 'nephrosis'. These should be as follows:

A. *Clinical.*

Chronic or elapsing oedema, with no cardiovascular changes (thus there are no retinal changes, no elevation of blood-pressure, and no cardiac hypertrophy).

B. *Chemical.*

1. Heavy albuminuria.
2. Absence of hæmaturia.
3. Oliguria is usually present, but there is no suppression of urine.
4. Doubly-refractile lipoids are often observed in the urine.
5. The basal metabolic rate is reduced.
6. The blood shows no change in its chemistry beyond—(*a*) a reduction of the plasma proteins, most marked at the expense of albumin fraction; (*b*) the frequent presence of a great excess of cholesterol.

C. *Morbid Anatomy.*

The rare cases seen *post mortem* usually die of pneumococcal peritonitis, and beyond the general pathological changes produced by this infection and by

[1] Received October 14, 1930.

the preceding oedema, show no gross abnormality except degenerative changes visible in the renal tubules when sections of the kidneys are examined microscopically.

Much of the difficulty which has prevented the acceptance, and indeed the understanding of the conception of 'nephrosis', has arisen from the fact that such cases are rare, whereas there is a very numerous group of cases, familiar to all observers, which resembles the rare cases in many particulars. This is the group which constitutes the 'chronic-glomerulo-nephritis' of the majority of writers. It is still described as 'chronic parenchymatous nephritis' in many British text-books.

It occurs as a sequel to many of the acute infective nephritides, and is the percursor of the 'secondary contracted kidney', which is seen many years after such initial attacks. In this disease it is admitted by the American and German observers that a primary glomerular lesion, of small apparent importance in its initial stages, may sometimes lead, perhaps after a period of haematuria and partial suppression of urine, to relapsing oedema with clinical and chemical manifestations indistinguishable from those occurring in 'nephrosis'.

But in such cases the course of time usually reveals some increase in the blood-pressure, hypertrophy of the heart, 'renal' retinitis, or increasing manifestations of renal insufficiency, till the patient ultimately dies either from renal failure or from effects of the cardiovascular changes. Post-mortem examination then invariably reveals glomerular as well as tubal change, and usually, perhaps always, evidence of the progressive as well as of the degenerative phase of inflammation of the kidneys.

In contrast to these, the cases of 'nephrosis' with full history and reports of the microscopy of the kidneys, obtained *post mortem*, are admittedly rare. Thus Fishberg (5), in his recent full description of the condition, only refers to two or three cases from his own observation in which post-mortem evidence has been obtained. Christian (8), writing in 1929, was able to trace only eighteen cases with post-mortem records from the literature, and Bell (9), also writing in 1929, collected but twenty-three from the literature, and added four from his own observation. Even when the cases of Kohn (10), of Cabot (11), of Rachmilewitz (12), and of Shapiro (13) are added, the total is not a large one. It is certain that a good many cases pass through the hands of morbid anatomists without being classified as 'nephrosis'; some of the cases of Dyke (14), of Russell (15), and of Gainsborough (16) undoubtedly fall into this category, and these series together probably yield at least six further examples of the condition under consideration.

But even if these additional cases are accepted, it is clear that the pathological material on which the conception can be based is meagre. The answer made to this criticism by those who support the conception of 'nephrosis' is that the majority of cases make a perfect recovery with suitable treatment; thus Epstein has reported cure in a number of cases, and observers such as

Clausen (4), Marriott (17), and Holt and Howland (18), whose experience is derived chiefly from children, appear to look upon the condition as relatively benign.

Our own experience does not agree with this. We have had little opportunity of studying the disease in children, but the examples we have encountered in adults have ultimately terminated fatally.

In the following sections of this paper will be found the full records of three cases which we believe justify the use of the term 'nephrosis', if this is ever permissible. In two of them death occurred relatively early, and the findings at autopsy clearly justify their addition to the eighteen recorded by Christian (8). The third, in the early months of his illness, was indistinguishable from the other two, and has been mentioned by us in previous communications (19). His ultimate course was one of renal failure. The discussion which follows the description of the cases gives our reason for including this case.

II. *An Account of Three Cases of 'Nephrosis'.*

Case No. 1. Nephrosis: death from pneumococcal peritonitis six weeks after onset.

Family history and early history. No history of hereditary taint, of renal disease, of scarlatina, nor of tonsilitis. 1917, mild attack of measles. 1919, operation for appendicitis, uncomplicated.

History of onset. On June 21, 1929, at the age of 33, patient had an attack of abdominal pain with diarrhoea, attributed to eating fresh salmon. Next morning he noticed swelling of the face, and soon afterwards the feet and ankles became similarly involved. By June 24th the swelling affected the whole of both legs. The abdominal disturbance ended after five days, but the swelling of the legs persisted. On July 8th, patient attended hospital. Oedema of both legs and scrotum, slight ascites, slight bilateral hydrothorax. Heart not enlarged; B.P. 102/126; urine S.G. 1020; massive albuminuria; no blood.

Condition on admission to hospital, July 22nd. Oedema of legs unchanged but spreading over the abdomen, chest, and back. Signs of fluid in the peritoneal and pleural cavities. Weight prior to illness, 118 lb.; present weight, 160 lb.; oedema, approximately 40 lb. Heart not enlarged; BP. 86/118; retinae normal; massive albuminuria; Wassermann reaction negative.

Treatment. Diet containing fish, eggs, biscuits, and vegetables in liberal quantities was prescribed; fluids not limited. Thyroid extract gr. 4 daily administered, the dose being rapidly increased up to 48 gr. daily, and stopped on the twelfth day on account of patient's condition.

July 27th. Patient had a rigor and vomited; temperature rising to 101°.

July 28th. Patient vomited once; persistent temperature of 100°; lower abdomen tender; B.P. unchanged; intelligence unimpaired.

July 30th. General condition had deteriorated; oedema increasing; pain on pressure over the legs and abdomen. Respiration was difficult, and it was decided that relief of the oedema was so urgently required that a series of incisions was made into each leg.

July 31st. Condition unchanged although several litres of fluid had drained from legs. A preliminary small dose of salyrgan, 0·25 c.c. of a 10 per cent. solution, with ammon. chlor. gr. 60, was given.

August 1st. Patient worse, cold and sweating, with oliguria; abdomen somewhat tender but not rigid; patient vomited slightly; respiration became difficult, and after a brief period of unconsciousness, without convulsions, death ensued.

Biochemical findings. 1. *Urine.* (a) *Volume.* When first observed the urinary volume varied between 400 and 600 c.c. daily. This rose during the succeeding days to between 1200 c.c. and 1500 c.c. daily, but fell in the terminal period of his illness to a figure of 400 c.c. or less.

(b) *Urea.* The urea content of a sample twenty-four-hourly specimen of urine averaged 2·7 grm. per 100 c.c. of urine during the first few days after admission, fell to an average of 0·7 grm. per 100 c.c. of urine as the volume rose to over 1400 c.c., and again rose to over 2·0 grm. per 100 c.c. of urine towards the end of his illness.

(c) *Protein content.* Estimations of the protein content of the urine were made on two occasions. On the first occasion, as an out-patient, a specimen of urine obtained was found to contain 36·9 grm. per litre of dried protein—30·7 grm. being albumin and 6·2 grm. being globulin. It was again estimated when the twenty-four-hourly volume of urine had reached 1120 c.c. This was found to contain 13·2 grm. of dried protein per litre, comprising 9·7 grm. of albumin and 3·5 grm. of globulin, this last representing an actual loss of 14·8 grm. of protein.

(d) *Blood.* At no time were red blood corpuscles detected microscopically.

(e) *Lipoids.* The centrifuged urine was several times examined for doubly refractive lipoids with negative results.

(f) *Glycosuria.* No sugar was found throughout the disease.

2. *Blood.* (a) *Nitrogen content.* The blood urea and non-protein nitrogen varied between 30 and 35 mg. per 100 c.c. of blood.

(b) *Chlorides, phosphorus, calcium, &c.* The chloride content of whole blood on three different occasions was 393, 403, and 383 mg. per 100 c.c. of blood. The phosphorus appeared normal and the calcium on the low side of normal, varying between 8·5 and 10 mg. per 100 c.c.

(c) *Cholesterol.* Hypercholesterolaemia, giving concentrations of 354, 376, and 300, was found. In the terminal stage of the illness the cholesterol fell to within normal limits, viz. 188.

(d) *Plasma proteins.* These were estimated only on one occasion, when the total protein of the plasma was found to be diminished to 2·97 grm. per 100 c.c. of plasma, 1·3 grm. of this being albumin.

3. *Oedema fluid. Post mortem* fluid was obtained from subcutaneous tissue, and from the peritoneal and pleural cavities, the actual analyses being as follows:—

	Ascitic Fluid.	Pleural Fluid.	Subcutaneous Fluid.
Urea in mg. %	93·2	71	88
Chlorides in mg. %	590	602	602
Total protein in grm. per litre	6·2	4·9	4·6
Calcium in mg. %	5·8	6·2	5·6
Phosphorus in mg. %	11·7	9·1	11·7

4. *Basal metabolic rate.* After correction to allow for increase of weight due to oedema fluid, the B.M.R. gave readings of −31 and −21 (using the Douglas Bag and the standards of Aub and Dubois).

Post-mortem findings. General oedema, 6 oz. clear fluid in right pleura, 16 oz. left; lungs poorly aerated, oedematous, bases congested. Peritoneum

contains two pints of fibro-purulent fluid, which on smear was found to contain pneumococci in large numbers.

Liver. 66 oz., fatty, with some congestion at centres of lobules.

Heart. Small (8 oz.), right side dilated; muscle somewhat soft and brown.

Aorta. Slight early atheroma.

Kidneys. (Right, 9 oz.; left, 9½ oz.); red in colour; when bisected showed some swelling of cortex, pattern indistinguishable in places, with fatty streaks and patches suggestive of areas of degeneration; pyramids appear healthy save for some congestion at base. Capsules strip readily, leaving a smooth surface with prominent stellate veins. Pelvis showed a small injected area ½ inch in diameter.

Histological appearance in kidneys. In paraffin sections there is very little abnormal to be seen. In many places the cell protoplasm of the convoluted tubules appears swollen and vacuolated. The glomeruli appear normal; there is no increase of interstitial tissue and no signs of any infiltration by inflammatory cells. Frozen sections stained with Sudan III show definite tubular damage. Many of the convoluted tubules show marked fatty changes, large and small globules of Sudan staining material filling the cells. The affected tubules occur in groups throughout the cortex. In the immediate vicinity of the fatty tubules there is much finely-granular fat contained in small spindle connective tissue cells lying between the tubules. A few hyaline casts are seen in some of the medullary tubules. The blood-vessels show nothing abnormal.

Case No. 2. Nephrosis: death from pneumococcal peritonitis one year and five months after onset.

Family history and early history. No history of hereditary taint. Patient believed that he had had slight childish ailments. Had never had scarlet fever, nor had he been subjected to sore throats.

History of onset. In November, 1929, at the age of 30, after years of good health, patient had a 'chill' and felt ill; thinks he had a severe cold, and probably slight pyrexia; temperature was not taken; no gastro-intestinal symptoms; remained at work although unwell for five weeks.

January, 1929. Observed ankles swollen one week, going down with rest. This recurred once or twice monthly until Whit-Monday (June, 1929), when after much walking both ankles and calves swelled. Got well until July, 1929, when again there was a few days' swelling.

August, 1929. Bad headache and pain in the back for three days, bowels a trifle loose, legs slightly swollen.

End of August, 1929. In camp on heavy meat diet, legs swollen. Consulted doctor, who found much albumin in urine; went to bed, legs subsided in three days, but albumin remained intense. Sent to University College Hospital, and was admitted, but discharged himself after a few days, believing that urea concentration test had upset him. Believes B.P. was 137.

October 13, 1929. Admitted Guy's. Blood urea 25. Albumin ++. B.P. 112. Returned home to his own doctor's care after investigation.

Condition when first seen by T.I.B. November 19, 1929 Patient in good general health, bowels rather constipated, passing 42–65 oz. daily, always with albumin, often intense albuminuria. Very slight oedema below knees, nil lumbar or facial region. B.P. 80/135; no cardiac hypertrophy. Weight 9 st. 4¼ lb. in clothes. Transferred to Out-Patients at Middlesex.

Subsequent progress.

December, 1929. Patient's condition was stationary, weight varied between 9 st. and 10 st., B.P, constant in the region of 90/145. During this period patient was kept under close observation, but remained at work and had no treatment whatsoever.

January–February, 1930. During this period there was a steady increase in oedema. In the middle of January this affected scrotum and penis. Abdomen rather full but without thrill; bases dull; pitting of tissues in lumbar and lower axillary regions; B.P. steady in the region of 90/145; retinae normal; no cardiac hypertrophy; thyroid medication gradually instituted and increased to 24 gr. daily. There was some embarrassment of respiration, and the pulse-rate was in the neighbourhood of 100. Patient still working, although oedema had now raised the weight from 9 st. 9 lb. to 11st. 6 lb.

Case 2. RES.

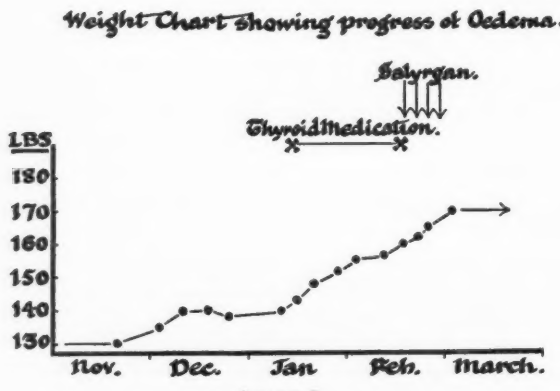

CHART I.

February 18, 1930. Salyrgan intramuscularly; thyroid stopped; this treatment was continued thrice weekly in increasing doses, but did not affect the steadily increasing oedema.

March 4, 1930. B.P. 104/176; weight, 12 st. 2½ lb.; oedema clearly increasing; urinary output fallen to 600 c.c. daily. Patient at this stage was still going to work daily and attending once or twice weekly at Out-Patients'. He felt very well, but the oedema had become so intense that he had to massage his legs in order to straighten them when he had been sitting for any length of time. It was clear that he was getting steadily worse, and that neither thyroid nor salyrgan had affected his condition, and he was therefore persuaded to come into hospital on March 5, 1930.

Progress after admission to hospital, March 5, 1930. Throughout his stay in the ward the patient remained in a condition of extreme oedema, affecting legs, arms, trunk, and, to a much lesser extent, the face; signs of bilateral hydrothorax remained as before. As regards the trunk the oedema was noticeably in the tissues of the abdominal wall and back, but on the second day after admission an obvious abdominal thrill developed which had not been present before. The heart appeared normal throughout. Blood-pressure in bed varied from 150 to 160 maximum systolic. On one occasion only, two days

before his death, it was observed at 190, but returned to 150 on the following day. The naked weight on admission was 162 lb.; it first increased a few pounds, then became stationary, and during the last week it declined about 1 lb. Corresponding with this, the urinary output, which on March 4th had fallen to 600 c.c., rose steadily until about March 14th, when it attained 1650 c.c. During the following week it declined again to 1200 c.c. on the 15th, and to 700 c.c. on the 18th, and 1000 on the 19th.

March 18, 1930. Temperature rose to 100° and patient vomited twice and complained of aching pain in the left side of the upper abdomen. The tissues were very tender to palpation; there was no abdominal rigidity. Pain and

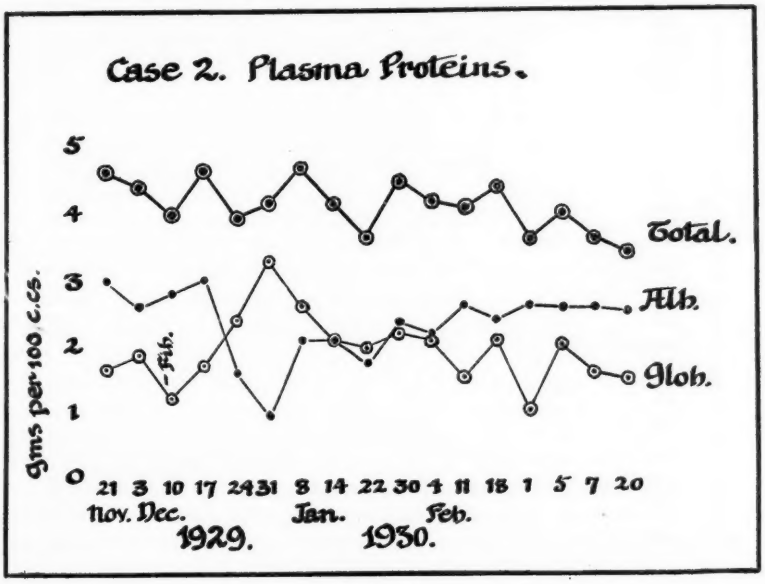

CHART II.

pyrexia increased on the following day, and ecchymoses became visible in both flanks; patient obviously very ill. This condition increased until death on the afternoon of March 21, 1930. The urine throughout his stay in the ward was kept definitely alkaline to litmus; it never was alkaline to phenolphthalein. After about six days' treatment he vomited once, and the face twitched readily on tapping; the dose of alkali was then diminished. At no time did any signs or symptoms of uraemia develop.

Biochemical findings. 1. *Urine.* (a) *Volume.* When first observed volume varied between 500 and 800 c.c. daily. This rose to an average volume of 1300 c.c., but in the terminal stage of his illness never exceeded 400 c.c.

(b) *Urea.* The urea content of a sample of the twenty-four-hourly specimen of urine at first averaged 1 grm. per 100 c.c. of urine. As the volume rose to 1300 c.c. the percentage of urea fell to 0·4, but again rose to 1 grm. per 100 c.c. of urine during the last days of the illness, when the volume averaged only 400 c.c.

(c) *Protein content.* Estimations of the total daily output of protein in grams of dried protein were made from time to time. This was found to vary from between 16 and 34 grm. daily.

(d) *Blood.* Red corpuscles were frequently found in specimens examined microscopically. The amount of blood was never sufficient to make the urine smoky, but a positive guaiacum reaction was sometimes found.

(e) *Lipoids.* The centrifugalized urine, though examined frequently for doubly refractive bodies, did not show any.

(f) *Glycosuria.* Sugar was often present, reaching a concentration of 1·5 per cent. in last few weeks of disease.

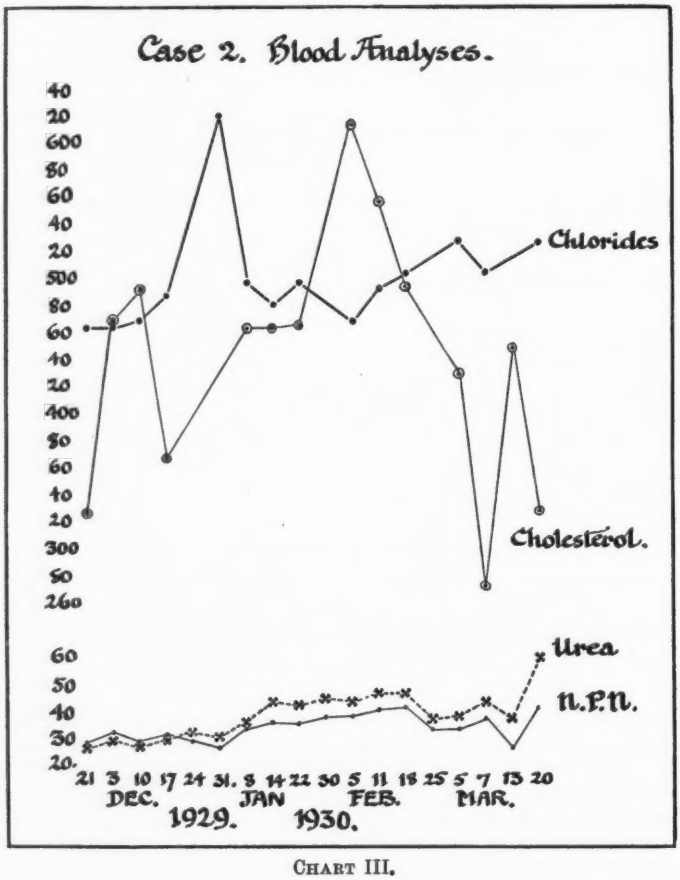

CHART III.

2. *Blood.* (a) *Nitrogen content.* The attached graph (Chart III) shows the readings for urea and non-protein nitrogen at different dates. There is a tendency for both to rise gradually throughout the course of the disease, but it was only a few days before death that the blood urea gave a single reading above 50 grm. per 100 c.c.

(b) *Chlorides, phosphorus, calcium.* The graph shows a tendency for the chloride content of the blood to rise. Phosphorus and calcium figures appear normal.

(c) *Plasma proteins.* The plasma proteins were diminished from the normal total of 7 to 8 to a value just under 5 when the case first came under observation. The graph shows that throughout the course of the disease the

total plasma remained at a fairly constant level of just under 5 grm. per 100 c.c. of plasma. During the progress of the disease the albumin figure showed a tendency to fall, and at the same time the globulin figure to rise, so inverting their ratio to maintain a constant summation, but in the final period it is to be noted that the albumin figure again exceeded that of the globulin.

3. *Oedema fluid. Post mortem*, fluid was obtained from the peritoneal cavity and subcutaneous tissue.

The actual analyses were as follows:—

	Ascitic Fluid.	Subcutaneous Fluid.
Urea in mg. per 100 c.c.	131	137
Chlorides in mg. per 100 c.c.	444	438
Calcium in mg. per 100 c.c.	7·6	4·0
Phosphorus in mg. per 100 c.c.	12·8	6·0
Protein	Trace	Trace

4. *Basal metabolic rate.* Estimated at a time when oedema was inconspicuous, this was found to be diminished by 10 per cent. (Benedict-Roth Apparatus used with the standards of Aub and Dubois).

Post-mortem findings. General oedema. About one pint of clear fluid in each pleural cavity; pericardium 2 oz., peritoneum 2 pints; limbs and subcutaneous tissues of trunk markedly oedematous. Tissue fluid and ascitic fluid grew pneumococci in large numbers; many present in indirect smear.

Lungs. Collapsed; slight oedema at base.

Heart. Small (7 oz.); no pericarditis; no valvular disease; no coronary disease.

Kidneys. Right, 8 oz.; left, 8 oz.; both organs somewhat enlarged. Capsules stripped easily, leaving a smooth pale cortical surface with prominent veins; on section a pale, slightly swollen cortex with indistinct pattern. Marked oedema of wall of renal pelvis.

Histological appearance of kidneys. Glomeruli practically normal; they showed no inflammatory lesions; sections stained for fat show a little fatty change in the endothelium of many of the tufts. The epithelium of the convoluted tubules is considerably flattened, and Sudan III stain shows fatty degeneration. Similar fatty changes are seen in the ascending limbs of Henle's loops. Some of the tubules contain a few red blood cells; there are also hyaline and a few granular and fatty casts. The interstitial tissue shows a general increase of fine fibroblastic connective tissue, so that tubules are separated from one another. In addition to the fibroblast increase there is a minor degree of infiltration of the interstitial tissue by plasma cells and lymphocytes.

Case No. 3. Nephrosis: relapsing oedema relieved by urea administration; gradual transition to hypertension and renal failure; death from uraemia two years after onset.

Family history and early history. No history of congenital syphilis.

1921. Mild attack of 'pleurisy'. No history of sore throats or renal disease.

History of onset. In August 1926, at the age of 22, whilst on summer holiday, and apparently in excellent health, patient observed abdomen and legs somewhat swollen. Fourteen days later observed swelling of face. Transient epigastric pain accompanied by diarrhoea.

Condition when first observed, October 27, 1926, seen at Out-Patients'. Middlesex Hospital. Marked swelling of abdomen with well-marked thrill, Signs of double hydrothorax; marked oedema of legs, heart not enlarged; B.P. 90/140; massive albuminuria.

On admission, October 29, 1926. B.P. 70/130: optic fundi normal. Wassermann negative. High protein diet together with 30 to 60 gr. of urea daily caused oedema to disappear almost completely, but evidence of slight ascites remained. Still had albuminuria on discharge, December 31, 1926.

January to March, 1927. Seen at Out-Patients': oedema fluctuating; weight rising slowly from normal 9 st. 10 lb. to 12 st. in spite of thyroid gr. 24 daily.

March 11, 1927. Second admission to wards. Findings in cardiovascular system as before. Massive oedema and albuminuria; under treatment with urea 100 to 120 gr., daily weight fell from 12 st. 1 lb. to 9 st. 12 lb. on discharge, April 12, 1927.

April 1927 to March 1927. Patient at work apparently much better; taking urea daily.

March 1928. B.P. 95/145; blood urea 79; N.P.N. 68. At this time the patient was demonstrated at the Royal College of Physicians as being apparently a case of nephrosis; it was pointed out (17) that a recent increase in the blood nitrogen had become apparent.

April 23, 1928. Unwell, cough, general pains; slight oedema legs, urea 92, N.P.N. 68.

May 7, 1928. Weight 10 st., better; very little oedema; B.P. 80/114. Patient was not seen again until *July 23, 1928,* when he was brought to hospital by ambulance, lethargic but conscious; four hours later became semi-comatose and had a violent fit; B.P. 90/170; urea 178; N.P.N. 111. He remained in semi-coma for two days with marked nitrogen retention, and then after another convulsion became unconscious with hyperpnoea and died on July 26, 1928.

Biochemical findings. 1. *Urine.* (a) *Volume.* In 1926, during the first week after admission, the volume varied between 700 and 800 c.c. daily. This rose to an average of 1,300 c.c. daily until his discharge some six weeks later. During admission in 1927 and again in 1928 there is unfortunately no record of the output of his urine.

(b) *Protein content.* In 1926 estimations of the daily output of protein were made from time to time, and this was found to vary between 14 and 20 grm. daily of dried protein.

In 1927. Estimations on specimens of urine obtained showed:

17.5.27.	Protein	=	6	grm.	per	1,000 c.c.
3.3.27.	„	=	4	„	„	„ „
19.3.27.	„	=	14	„	„	„ „

Owing to lack of information of the volume of urine excreted the total daily output of protein is not estimable.

In 1928. 24.7.28. The amount of protein in a specimen of urine obtained is given as +.

(c) *Blood.* Blood both microscopically and by the guaiacum test was found in 1926, but there is no record of its presence in 1927 and 1928.

(d) *Lipoids.* Though the presence of doubly refractive lipoids were sought for in the centrifugalized urine, it cannot be said with certainty that they were seen.

(e) *Urea. 1926.* The urea content during the first week of admission was 2·0 grm. per 100 c.c. of urine. It fell to 1·0 grm. per 100 c.c. as the daily volume increased.

1927. No report on urea.

1928. The urea content was 0·6 grm. per 100 c.c. of urine, but as this was not a composite sample of the 24-hourly specimen it is of doubtful value. Patient was frequently incontinent during this period.

(f) *Glycosuria.* This was never present.

2. *Blood.* (a) *Nitrogen content.* The attached graph shows the readings of the non-protein nitrogen and urea at different dates in 1926, 1927, and 1928. It will be seen that during his first admission in 1926 his nitrogen figures are within normal limits. In the early part of 1927 they are still normal, but in December 1928 the urea had risen to 79 mg. per 100 c.c. During 1928 nitrogen figures continued to rise, ultimately reaching a blood urea of 268 and a non-protein nitrogen of 220 a few hours before the disease reached its fatal termination.

(b) *Chlorides, calcium, and phosphorus.* The figures for chlorides are:

2.11.26.	479	mg.	per	100	c.c.
11.11.26.	429	„	„	„	„
24. 3.27.	528	„	„	„	„
7.12.27.	649	„	„	„	„
5. 3.28.	610	„	„	„	„
23. 4.28.	485	„	„	„	„
23. 7·28.	608	„	„	„	„
24. 7.28.	590	„	„	„	„
25. 7.28.	608	„	„	„	„
26. 7.28.	585	„	„	„	„

There is a tendency for an increase in the chloride content of the blood. The calcium figures show a peculiar variation, viz.:

5.3.28.	11·8	mg.	per	100	c.c.
23.4.28.	7·6	„	„	„	„
24.7.28.	7·7	„	„	„	„
25.7.28.	7·9	„	„	„	„
26.7.28.	10·6	„	„	„	„

The phosphorus figures are on the high side of normal, averaging 5·5 mg. per 100 c.c.

(c) *Cholesterol.* Typical figures were 209, 256, 246, 294, 244. The figures tended to fall as the fatal termination was reached, the last figure being 190.

(d) *Plasma proteins.* These were not estimated.

3. *Oedema fluid.* This was found to be diminished by 14 per cent. (Douglas Bag used.)
(Standards of Sandborn.)

Post-mortem findings. No oedema; body-weight 138 lb. No fluid in thorax; 10 oz. clear fluid in peritoneal cavity.

Lungs. Oedematous and congested throughout; terminal broncho-pneumonia at both bases.

Brain. Some flattening of convolutions; slight increase of fluid in ventricles.

Heart. Weight 12 oz.; some hypertrophy left ventricle; valves and myocardium nil, abnormal; coronary arteries patent, slightly atheromatous.

Aorta. Slight early atheroma.

Kidneys. Right 5 oz., left 5½ oz. Both organs somewhat enlarged. Surface pale and finely granular; on section pattern indistinct; parenchyma very pale; cortex white; pyramids pale pink with numerous light yellow streaks running over them from apex to base; slight diminution in width of cortex.

Histological appearance of kidneys. The kidney capsule is somewhat thickened and blends in places with the denser areas of interstitial tissue at the cortical surface.

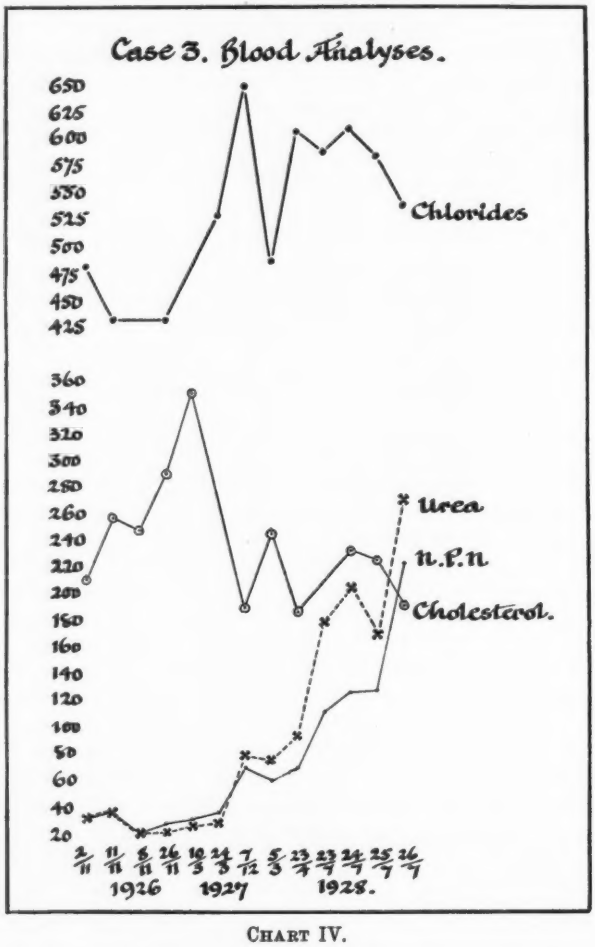

CHART IV.

Groups of large dilated and thinned convoluted tubules are separated from one another by areas of dense cellular connective tissue showing much lymphocytic infiltration. In the denser portions of the connective tissue the tubules are reduced to atrophied remnants. In sections stained with Sudan III fatty degeneration is present in a few groups of convoluted tubules but the majority are free from fat. Where the fatty change is marked a slight amount of doubly refractile material is present; the medullary tubules contain numerous granular casts, some fatty debris, some red blood-cells and occasionally a few leucocytes. Many of the glomeruli are involved in the areas of dense connective tissue and lymphocytic infiltration; in these the most striking change is an ischaemic atrophy associated with a marked fibrous thickening of Bowman's capsule. In many of these areas the glomeruli are completely atrophied. In a certain number there is marked fatty degeneration of the endothelial cells of the tuft.

Of the glomeruli that are more or less free from ischaemic change few, if any, are normal. Adhesions between the tufts and the wall of Bowman's capsule are present to a greater or less extent in nearly every case. This is associated with a hyaline necrosis involving one or more lobules of the tuft. Cellular proliferation within Bowman's capsule is not seen.

There is a general increase of collogen-forming connective tissue which separates the renal elements throughout the kidney, in addition to which, as mentioned above, denser strands heavily infiltrated by lymphocytes extend to the cortical surface.

The larger vessels show no definite thickening or narrowing. In places an interlobular artery with fatty degeneration and narrowing of the lumen is seen and a similar fatty change can be detected in the glomerular arterioles.

III. *Commentary.*

A. *Clinical.* Judged by clinical standards these three cases appear to be examples of the same disease. Three men aged 33, 30, and 22 are each suddenly aware, after years of good health, that their legs are swelling. On seeking medical advice each is found to have a heavy albuminuria and oedema of the lower part of the legs, but no other evidence whatsoever of disease. In each the oedema increases, becomes generalized, with fluid in the pleural and peritoneal cavities. The blood-pressure remains normal and the blood and urine show no evidence of any reduced renal excretory function. In two of the cases there was an apparently trivial attack of abdominal pain accompanied by diarrhoea in the early weeks of the disease.

In one instance, six weeks after the onset of this illness, and in the second instance over a year after onset, a pneumococcal infection of the oedematous tissues occurs and terminates the life of the patient. In the third case the oedema subsides as the result of treatment, recurs later after a period in which albuminuria was the only evidence of disease, is once more relieved by treatment, but subsequently, about eighteen months from the beginning of the disease, the patient begins to manifest renal insufficiency with some rise of blood-pressure. During the subsequent five months oedema disappears, the non-protein nitrogen of the blood increases, and patient is finally admitted into hospital in uraemic coma, to which he succumbs.

B. *Biochemical.* The first of these two cases, and the third in its early stages, appear to present biochemical features in general accordance with those described by Epstein and others as characteristic of nephrosis. In certain details there is some departure from the picture as usually described, but this may be due to more stringent criteria adopted by ourselves. The main facts have been recorded with the description of each case, and regarding them as a group—that is to say, Cases no. 1 and 2 throughout the period of observation, and Case 3 during the first eighteen months of observation—the following points call for comment:

1. *Urine.* (a) *Volume.* The average volume passed is somewhat below the normal rising to a figure well above the normal at periods when oedema is arrested or diminished.

(b) *Urea.* The concentration of urea secreted in the urine of these patients conforms to that seen in normal subjects.

(c) *Protein content.* The output of protein in the urine is very large, amounting to upwards of 30 grm. (estimated as dried protein) per diem, on many occasions. We have failed to find any evidence to suggest that this protein is qualitatively different from that of the plasma proteins. Albumin is always predominant, and using the most exact quantitative methods of analysis at present available it is clear that the total loss of albumin in these cases is an amount equivalent to the whites of 5, 7, 10 or more eggs every day, and that this depletion is continued for months.

(d) *Blood.* In two cases the presence of red blood corpuscles was noted in the urine on many occasions. This was determined by centrifugalizing about 20 c.c. of a mixed twenty-four hourly specimen and examining the deposit under the microscope. The presence of even a few red blood corpuscles was regarded as 'blood positive'. There was no macroscopic suggestion of blood in the urine, and but for the very careful microscopical test its presence would have been missed. The significance of a few red cells in the deposit from a twenty-four-hourly specimen is not fully understood, and we feel that their presence in no way excludes our cases from the group of 'nephrosis'. In the published literature the usual statement is that blood has been seen or not, and unless the technique of the test employed is given it is impossible to assess the importance of it.

(e) *Lipoids.* A careful search was made in each case for lipoid bodies in the urine. The technique employed was the examination of centrifugalized films with a polarizing microscope. It is possible to find such bodies in many normal urines, and particles giving the phenomena of double refraction are also common in the urine from patients of the type under consideration. It was decided, however, to regard as significant only those bodies which showed double refraction when they were actually inside the cast, and, adopting this perhaps over-severe criterion, we have been unable to detect such bodies in any of the cases here considered.

2. *Blood.* (a) *Nitrogen content.* Cases 1 and 2 showed no nitrogen retention at any stage save in the last few days before death, when in Case 2 the figures rose above 50 mg. In Case 3 the final months of the disease were marked by progressive nitrogen retention.

(b) *Chlorides, phosphorus, calcium.* The chlorides showed a tendency to increase in concentration in the later stages of Cases 2 and 3, but existing methods for the estimation of the blood chlorides are not such as to enable us to draw deductions, but in no case was there massive chloride retention.

Phosphorus and calcium were approximately normal in all three cases, though there was an inexplicable variation in the calcium readings in Case 3.

(c) *Cholesterol.* Each of the three cases showed hypercholesterolaemia.

(d) *Plasma proteins.* In Cases 1 and 2 there was very definite reduction in plasma proteins the total plasma proteins being below five in each case.

The reduction was more marked at the expense of the albumin fraction, but there was no constant reversal of the normal proportions of albumin and globulin. Discussion of these facts is reserved for a later paper now being prepared.

3. *Oedema fluid.* Oedema fluid recovered *post mortem* from the peritoneal and pleural cavities and from the subcutaneous tissues in Cases 1 and 2 was notable in each instance for the small amount of protein it contained. The lowest protein was in each case found in the subcutaneous fluid.

4. *Basal metabolic rate.* It is worthy of comment that the reduction in the basal metabolic rate in these three cases was less than published observations on 'nephrosis' would lead one to expect. When it is noted that the experimental error in such observations amounts to about 15 per cent., and when it is admitted that in apparently healthy people basal metabolic rates as low as −20 per cent. are quite commonly encountered, it appears that the evidence of marked reduction of basal metabolic rate in these cases is imperfect. The published figures in the review by Bell (13) do not support the view that reduction of the basal metabolic rate is a very conspicuous feature of 'nephrosis'.

C. *Histological.* On histological evidence there appears to be little doubt that Case 1 and Case 2 represent different stages of the same type of renal damage. The lesion is almost entirely tubular in both cases, but in Case 2 it has reached a more advanced state; there has been time for considerable loss of the ordinary tubular epithelium with the establishment of a more flattened type of cell and for the development of proliferative changes in the interstitial connective tissue.

In Case 3, the histological evidence of this being a sequel to the condition seen in Case 2 is lacking. Apart from the secondary ischaemic changes, the glomerular lesions, although practically universal, represent the effects of a comparatively gradual change without violent inflammatory phenomena. The process as a whole must have been comparatively slow, and it is possible that a pure tubular lesion was present initially. Examples of many intermediate stages would, however, be required to demonstrate a transition between the renal condition of Case 2 and that of Case 3.

Six months before his death Case 3 was indistinguishable, by any known test, clinical or biochemical, from Cases 1 and 2, but at that date his kidneys must, from an anatomical point of view, have already been grossly different in that considerable glomerular and interstitial change must have already been present.

Section IV. Conclusions.

A study of the two preceding sections must, we feel, lead to the conclusion that Case 1 and Case 2 belong without question to the group which has been described as 'nephrosis', and of which, as we have shown in the introductory

section of this paper, not more than thirty have been described in the literature. The recording of these cases is the primary object of this paper.

The clinical aspects of Case 3 in its terminal stages and the morbid anatomical features after death present a widely different picture to that given by Cases 1 and 2. We feel a most important problem emerges from this: *Does this case, or does it not, belong to the same group as the two preceding ones?*

It is usually left to the morbid anatomist to answer such a question, and the reply is almost invariably an emphatic negative. We strongly suggest that though such a reply is natural in view of the microscopic appearances confronting him, it becomes illogical and insufficient when all aspects of the case are fully reviewed.

The macroscopic and microscopic appearances of the kidney in this case are perhaps indistinguishable from those seen in the late stages of nephritis following an initial glomerular lesion. Examples showing intermediate stages between the lesions visible in the kidneys of Cases 1 and 2, and those seen in the kidneys of Case 3, are unknown to us, nor have we found them described in the literature. It by no means follows that further research will not eventually lead to the production of such examples.

Death in renal disease, if directly due to the renal lesion, is invariably the result of destruction of a large proportion of the total number of functioning glomeruli, and it therefore follows that unless death be due to some intercurrent disease, or to some secondary effort of renal disease (such as infection of oedema fluid), the pathologist must obtain specimens exhibiting advanced glomerular destruction; but to assume from this that a specimen in which glomerular destruction is conspicuous must have exhibited glomerular lesions from the outset is, we maintain, illogical.

It is perhaps useful to ask the following question: Given severe damage to the tubal epithelium alone, without glomerular lesions, what will be the fate of the kidney in the future? It seems clear that one of three effects must be produced:

(*a*) Complete resolution with restoration of the patient to permanent good health;

(*b*) An arrest of the progress of the disease without resolution, when presumably the patient will remain stationary from a clinical point of view; or

(*c*) Progressive change, which must eventually produce severe effects on the glomerulus and ultimately tend to the death of the patient with nitrogen retention and the other phenomena of renal failure.

We suggest that this is what occurred in Case 3, which was the late sequel of the same pathological process which produced the effect seen in the sections from Cases 1 and 2. We further suggest that many cases of 'secondary contracted kidney' dying of uræmia may very well have the same origin.

We wish to express our indebtedness to our colleague, R. W. Scarff, for the numerous microphotographs he has prepared for us, some of which are reproduced with this paper.

Summary.

1. Less than thirty cases of 'nephrosis', with full post-mortem data, are to be found in the literature.

2. The clinical, biochemical, and pathological features of two further cases are described.

3. A third case, identical with these in the early stages of the disease, but terminating with uræmia, and exhibiting different pathological features, is also described.

4. It is suggested that this third case, on the insufficient facts now available, may be considered as belonging to the same group as the previous two.

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FIG. 1. Case I. Paraffin section. Stained with haematoxylin and eosin. × 75. General view of part of cortex. Several glomeruli of normal appearance. No increase in intertubular connective tissue.

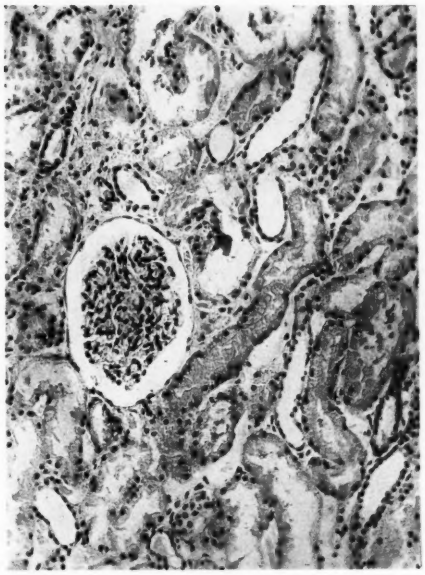


FIG. 2. Case I. The same section as Fig. 1. × 150. A glomerulus of normal appearance. Tubular epithelium showing a vacuolated appearance; shown by Sudan III stain to be due to fatty change. Photographed with defraction.

FIG. 3. Case I. Another field from the same section as Fig. 1. Fatty changes in tubular epithelium.

FIG. 4. Case I. Higher power (× 250) of glomerulus seen in Fig. 2.

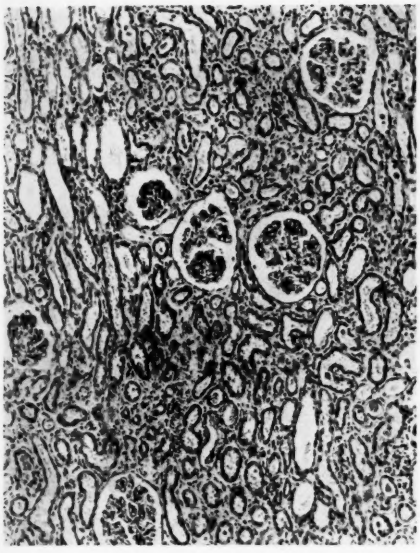


FIG. 5. Case II. Paraffin section. Stained with haematoxylin and eosin. × 75. The flattening of the tubular epithelium and the general increase of intertubular connective tissue is well seen.

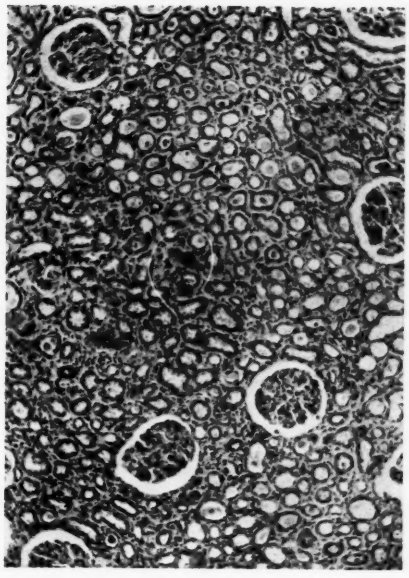


FIG. 6. Another view of the same section as Fig. 5. Glomeruli of normal appearance. Intertubular connective tissue increased.

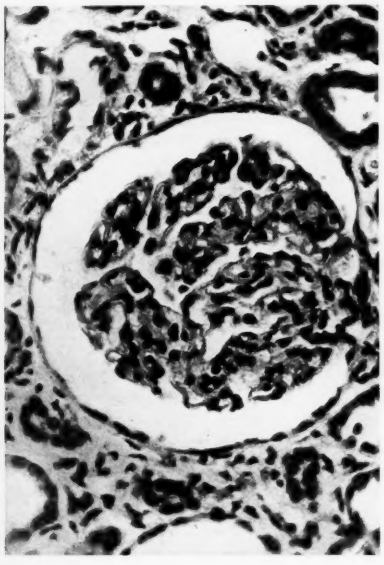


FIG. 7. Case II. Higher power. × 350. A glomerulus from the same section. No evidence of inflammatory change.

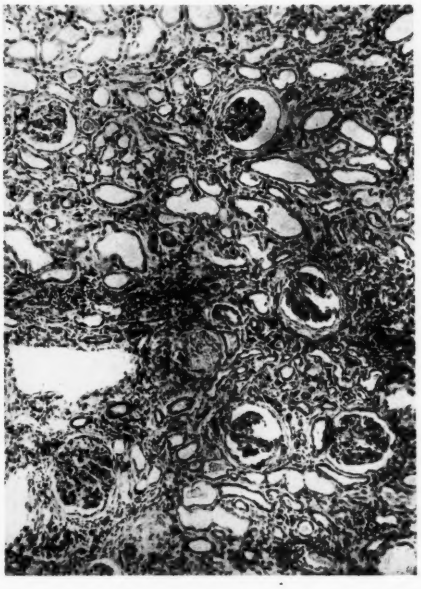
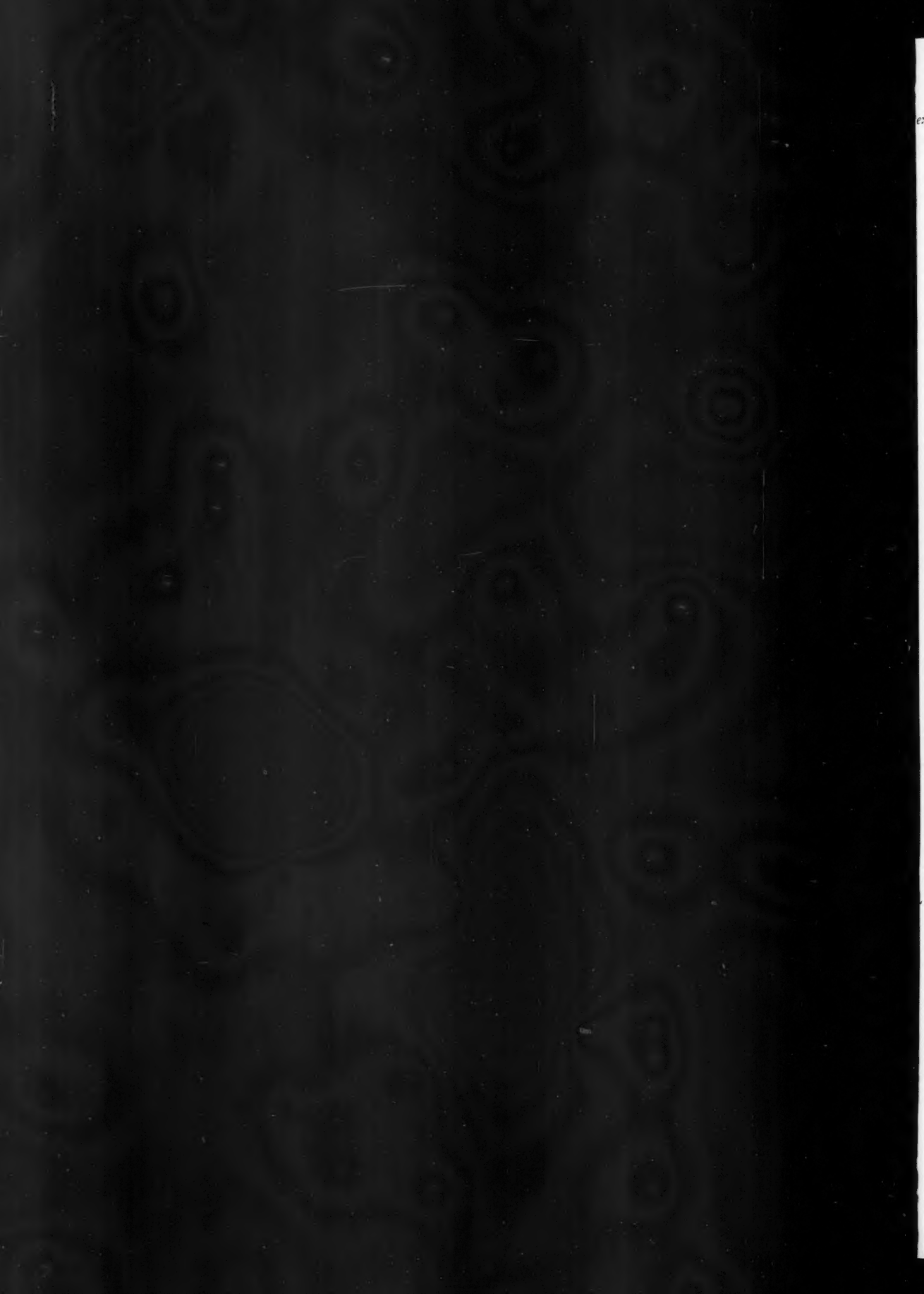


FIG. 8. Case III. Low-power view of a paraffin section. Marked glomerular and interstitial changes with collections of large tubules lined by flattened epithelium.



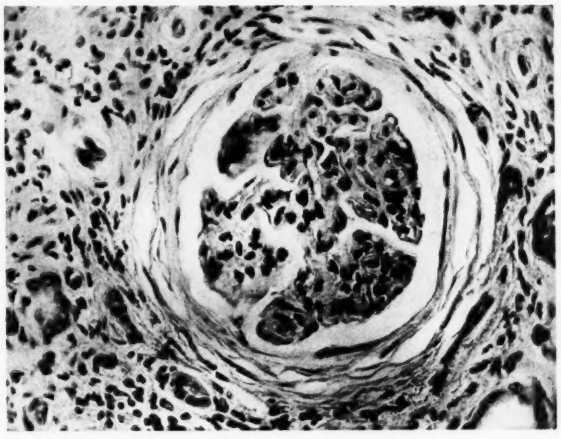


FIG. 9. Case III. Paraffin section. Stained with haematoxylin and eosin. High power (× 350) view of glomerulus, showing fibrous tissue thickening of Bouman's capsule.

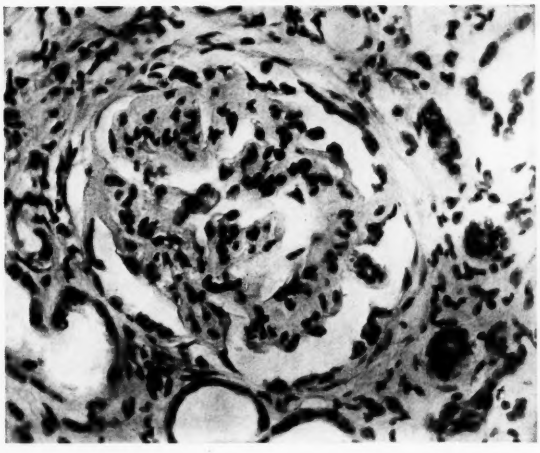
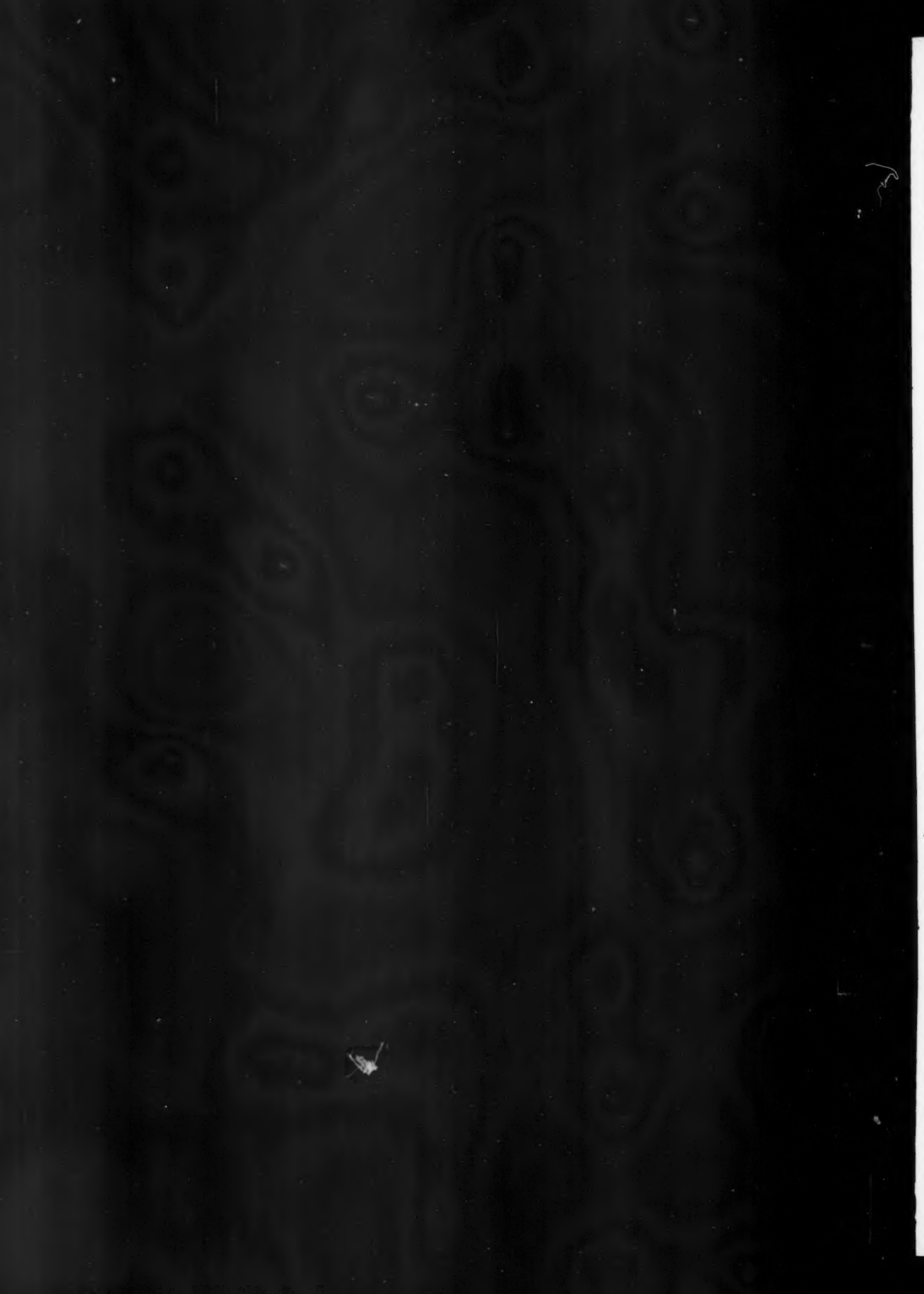


FIG. 10. Case III. The same section and magnification as Fig. 8. A glomerulus showing adhesions to Bouman's capsule.



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THE SUGAR-CONTENT OF THE BLOOD IN ELDERLY PEOPLE[1]

By F. W. MARSHALL

Of late years, the behaviour of the blood-sugar after the ingestion of a quantity of glucose has come to assume considerable diagnostic significance, and the Glucose Tolerance Test is now well known. The usual method adopted is to estimate the blood-sugar of the patient after a three to four hours' fast. Fifty grams of pure glucose are then given dissolved in about 150 c.c. of water, and the blood-sugar is thereafter estimated every half-hour for two hours. A curve is thus obtained which in a true case of diabetes mellitus is quite typical. The questions of the type of sugar tolerance curve found in the non-diabetic person and any variations found in other diseases have been the subjects of numerous investigations by observers in all parts of the world.

The effect of age on the type of curve elicited has also been investigated, but unfortunately the type of curve found in elderly people seems to have received little attention. This is probably explained by the fact that it is not easy to collect a sufficient number of aged people to form the basis of such an investigation. The author has had access to the inmates of a moderately large Union Workhouse and Infirmary, and it seemed to him that such an opportunity for investigation on this subject was not to be neglected. The following paper is based on investigations carried out on fifty elderly people, all of whom were inmates of this Institution, and who could therefore be kept under fairly close observation.

Method of selection of cases. The only qualification for admission to the series has been that the subject should be over 65 years of age. The ages, therefore, vary from 65 in the case of the youngest subject to 94 in the case of the eldest. The average age is 72 years. The series consists entirely of men, but the only reason for this was that for the purposes of the investigation men were much easier to deal with than women, and specimens for examination of the urine could be obtained with greater ease and certainty.

Technique. A preliminary clinical examination was made in each case and special note was made of the teeth, cardiovascular system, including the estimation of the blood-pressure, respiratory system, and the alimentary system.

The method used in the estimation of the blood-sugar was that devised

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by Maclean (1). Its accuracy in the author's hands was repeatedly checked by the estimation of standard solutions of glucose and by the estimation of the author's own blood-sugar. No ground for doubt as to the accuracy of the method was ever found.

The Glucose Tolerance Test was performed as follows: Each man had his breakfast in the ordinary way at 7 a.m. No further food was allowed until after the test had been completed. At 2 p.m. the blood-sugar was estimated, the urine tested for sugar and acetone, and 50 grm. of powdered glucose given dissolved in 200–300 c.c. of tap water. It has been stated (2) that the amount of fluid given appears to exercise little if any influence on the shape of the curve, and accordingly, whenever possible, the glucose was dissolved in a large volume of water in order to encourage diuresis. This was found to be very necessary in the type of case under consideration, as, even when a considerable quantity of water had been given, a good deal of difficulty was often experienced in obtaining specimens of urine for examination. Samples of blood, for blood-sugar estimation, were then taken every half-hour up to $2\frac{1}{2}$ hours from the time of the glucose feed. It was found at the outset that any period under two hours was quite useless, as in the large majority of cases the blood-sugar had not settled down to the fasting level until at least two hours had elapsed from the time of the glucose feed.

In the majority of the cases a specimen of urine was obtained at the end of the first, second, and fourth hours. These specimens were tested for sugar by Fehlings method and for acetone by Rothera's sodium nitroprusside method. In cases were sugar was found in the urine it was estimated by Benedict's quantitative method.

In most cases a 24-hour specimen of urine was obtained while the subject was on his ordinary diet, and the quantity and specific gravity of this were measured, and it was tested for albumin, sugar, and acetone. It may be noted that, although each specimen of urine obtained was tested for acetone, a positive reaction was never seen, and the fact that the urine was so tested is, therefore, omitted in the description of the individual cases in the appendix.

The Normal Blood-Sugar in the Healthy Adult.

Before discussing the results obtained in this investigation it is necessary for comparison to consider briefly some of the literature on the subject of the Glucose Tolerance Test and the type of curve found in the healthy young adult. In 1913 it was shown by Jacobson (3) that, following a carbohydrate meal, the blood-sugar rises sharply to a maximum level of 0·16 or more, which is reached in 30 minutes. It then falls more gradually to its original level, the whole reaction occupying from one to three hours. In 1918 Sakaguchi (4), using Bang's method, investigated the blood-sugar in healthy young adults following the ingestion of 100 grm. of glucose. He noted that a rise of blood-sugar was appreciable in 10 minutes, and that the maximal height, varying between

0·133 per cent. and 0·191 per cent., was reached within 20–40 minutes. Thereafter the blood-sugar subsided quickly and returned to its normal level in from 50 to 90 minutes from the time of the glucose feed. Hamman and Hirschmann (5), using the Lewis Benedict method and giving 100 grm. of glucose, established that the normal renal threshold varies between 0·17 per cent. and 0·18 per cent. They showed that in normal persons the blood-sugar rises promptly to a level not exceeding 0·15 per cent., this high point being usually reached in 30 minutes. From this high point the blood-sugar gradually falls off to its original fasting level, the whole reaction taking from one to two hours.

In 1921 MacLean and De Wesselow (2) described the methods of performing the Glucose Tolerance Test, and compared the curves obtained in normal adults with those obtained in diabetics. They recommended that the test should be performed after a three to four hours' fast, and stated that for general use a dose of 50 grm. of glucose was adequate. Indeed, they showed that in the case of definite diabetes a much smaller dose of glucose was amply sufficient to produce a typical reaction. They stated that, as a working rule, if the blood-sugar fails to return to its original level within about 1½ hours after a single 50 grm. dose of glucose, a defect of storage may be considered to be present. This statement is of considerable interest in view of the findings about to be described, as it will be shown that in old age there is, in the large majority of cases, a very considerable storage defect.

The question of the variations of the sugar tolerance found at different ages was considered by J. C. Spence (6) in a paper published in 1921. He showed that the same degree of sugar tolerance is not constant at all ages, being greatest in infancy, and tending to become lessened as age advances. In children under three years a low sugar curve is stated to be the expression of the normal sugar tolerance, but above this age the curve resembles that of the young adult. Curves were obtained from five men over 60 years of age, and four of these showed a marked diminution of sugar tolerance with consequent hyperglycaemia. It is pointed out that of these five cases two only had a normal fasting level, and these were in hospital convalescing after minor operations, and on a somewhat restricted carbohydrate diet. The other three cases had each a high fasting blood-sugar and appeared to be living in a state of persistent hyperglycaemia.

The Glucose Tolerance Test in health was considered from various aspects by Hale White and Payne (7). These authors paid special attention to changes occurring in the curve in old age. They investigated fourteen cases in this class, of which ten were over 70 years of age, and four were between the ages of 50 and 70. Of the subjects over 70 years of age, five gave curves with a peak over 0·21 per cent. None of the cases between the ages of 50 and 70 gave a high peak. Most of the fourteen cases showed some delay in returning to the fasting level. The authors therefore concluded that certain changes take place in the sugar tolerance curve in old age, there being a higher rise and a slower fall. They suggested that a peak of 0·22 per cent. at the age of 70,

rising to 0·24 per cent. at the age of 80, may be considered as normal, and that the time taken for the blood-sugar to return to normal should be within three hours for those over 60 years of age. These results, as will be seen later, are amply supported by the cases to be described, and in fact the higher rise and slower fall of the blood-sugar in old age, noticed by Hale White and Payne, are two of the most striking points brought out by this investigation.

Results.

The results of this investigation on the sugar-content of the blood in elderly people will be considered in detail. The notes and curves of each individual case will be found in the Appendix.

The cases are analysed according to their clinical diagnoses in Table I, and it is proposed to consider first the curves of the healthy subjects. Subsequently the curves encountered in the unhealthy subjects will be discussed.

TABLE I.

Clinical Diagnosis.	Number of Cases.
Healthy old men	28
Senility	5
Chronic bronchitis (severe)	5
Cardiac disease	3
Rheumatoid arthritis	2
Chronic osteitis of tibia	1
Senile gangrene of toe	1
Tuberculous neck sinuses	1
Carbuncle of back	1
Parenchymatous goitre	1
Carcinoma of oesophagus	1
Carcinoma of prostate	1

The sugar tolerance curve in healthy old age. Twenty-eight cases are shown in Table I as being healthy old men, and the curves of these are important, because they give some indication of the types of curves which may normally be met with in persons over the age of 65. Five types of curve are met with, and these types, and the numbers of the cases which illustrate them, together with the percentage incidence of each type, are shown in Table II.

TABLE II.

Type of Curve.	Case Numbers.	Incidence %.
Normal adult curve	13, 24, 33, 39	14
Storage defect	5, 8, 9, 11, 16, 17, 19, 28, 42, 47, 49	39
'Lag' curve	7, 12, 20, 36, 38, 45, 48	25
'Flat' curve	32, 50	7
Typical diabetic curve	14, 18, 35, 44	14

Each of these types will now be considered in detail.

I. *Curves Approximating to the Typical Normal Adult Curve.*

The normal adult curve is taken as being one in which the blood-sugar rises from a fasting level of about 0·1 per cent. to a maximum of 0·17 per cent. in from half to one hour from the time of the glucose feed. The blood-sugar then falls, and in one and a half hours has reached, or almost reached, its fasting level. As a rule, by two hours, the blood-sugar has fallen to below its original fasting level. Four cases of this type are present. Their curves are, perhaps, rather more exaggerated, both in height and length, than the typical curve described, but they can, nevertheless, be fairly included in this category. It is noteworthy that the percentage incidence is as low as 14 per cent.

II. *Curves Showing a Storage Defect.*

These curves are important as they indicate the marked alteration in the storage mechanism which may occur in old age. It is well known that the principal storehouse for glucose in the body is the liver. Glucose is also stored in the muscles, but their function in this respect is less important than that of the liver. The sudden fall which occurs in the blood-sugar of a healthy young adult, half an hour after it has risen in response to, say, a fifty gramme dose of glucose, is explained by the rapid conversion of glucose into glycogen by the liver, in which state it is stored by this organ. In the average subject any disturbance of this glucose storage mechanism, as shown by a lengthening of the glucose tolerance curve, is regarded with grave suspicion, and may be taken, in most instances, as an indication of potential diabetes mellitus. In the aged, however, a like significance cannot be attached to such a lengthening of the curve, because, as Table II shows, about 39 per cent. of normal, healthy people over the age of 65 show a defect in storage, when the sugar tolerance curve is estimated. For the purposes of this table, a storage defect has been taken as being present, when the blood-sugar has failed to return to its normal fasting level within two hours from the time of the glucose feed. Eleven such cases are present.

III. *The 'Lag' Curve.*

The so-called 'lag' curve is a well-known type of curve which is occasionally found in the apparently normal adult. A brief description of it, as usually met with, may not be out of place here. Occasionally, in patients suffering from considerable glycosuria, the blood-sugar, two hours after a dose of glucose, is quite low. These patients may be cases of an abnormally low renal threshold. Sometimes a very peculiar type of curve is met with described by Maclean (1) as follows. The blood-sugar, starting from a fasting level of 0·10 per cent., rises quickly in half an hour to 0·214 per cent. At the end of one hour it drops to 0·154 per cent., and at the end of one and a half hours it reaches the level of 0·098 per cent. The urine at the beginning of the test shows a trace of sugar,

and the sample passed at the end of the test contains 0·18 per cent. of sugar. It will be seen, therefore, that the mechanism for dealing with glucose was quite active in this case, as shown by the fact that the blood-sugar reached a point below the fasting level in one and a half hours from the time of the commencement of the test. In the normal subject, however, there is also a mechanism which in some way prevents the blood-sugar from exceeding the threshold value, and in the type of case under consideration this appears to be absent. As regards the diagnostic value of the 'lag' curve little is known, but it is generally held that, provided that there is no delay in returning to the normal level after glucose, there is probably no gross disturbance of the carbohydrate mechanism. It is reasonable to expect that if this type of curve is found in the young subject, it should also be met with in elderly people, and if it is indicative of a potential breakdown in the carbohydrate metabolism, one would expect it to occur with increasing frequency in old age. Unfortunately, no statistics are available as to the frequency with which this type of curve is found in the normal adult. It would appear, however, that its occurrence is very infrequent.

In the twenty-eight healthy cases examined, a 'lag' type of curve was observed in seven instances. Table III gives the details of these cases.

TABLE III.

Case No.	Age.	Fasting B. S.	Blood-sugar.					Sugar in Urine During Test.
			½ Hr.	1 Hr.	1½ Hrs.	2 Hrs.	2½ Hrs.	
7	73	0·112	0·162	0·231	0·175	0·106	0·086	Absent
12	66	0·100	0·268	0 231	0·131	0·118	0·106	Present
20	66	0·106	0·193	0·237	0·125	0·093	0·068	Absent
36	77	0·075	0·231	0·162	0·125	0·068	0·050	Absent
38	68	0·112	0·225	0·212	0·137	0·068	0·050	Present
45	68	0·137	0·143	0·225	0·150	0·112	0·075	Absent
48	74	0·118	0·156	0·193	0·200	0·081	0·075	Present

This table shows, in the first place, that, with the exception of Case No. 45, the fasting blood-sugar in each case is at about the normal level. In all cases it has returned to the region of the fasting level in two hours, thus showing that no storage defect is present. Secondly, although the rise is quite as high as in the ordinary 'lag' curve, in four of the seven cases it takes longer than usual to attain its maximum level. In no case has the blood-sugar returned to its fasting level within one and a half hours, as would be expected in the ordinary case of this type. In three cases only did glycosuria occur during the test, and in none of the cases was sugar present in the ordinary twenty-four-hour specimen of urine.

It would thus appear that in elderly people the 'lag' curve tends to occur more frequently than in the young adult. In this series it occurs in 25 per cent. of the healthy cases. Such a high incidence may be taken to mean that the 'lag' type of curve is an indication of a commencing fatigue, as it were, of the mechanism for dealing with carbohydrates. On reviewing the curves of the remaining twenty-two cases, of the series tested, which have been shown as

suffering from one or other of the diseases named in Table I, only one curve—that of Case No. 4—can be regarded as in any way a typical 'lag' curve. It is therefore likely that the strain imposed on the mechanism for dealing with carbohydrates, by the presence of some pathological condition, converts the 'lag' curve of healthy old age into a more abnormal type of curve by producing a storage defect, and for this reason the 'lag' curve is not met with in old age, when the subject is suffering from any gross pathological condition.

IV. *The 'Flat' Curve.*

It is known that glucose taken by the mouth is not absorbed until it reaches the small intestine. Here the majority of it is absorbed direct into the portal circulation and is conveyed thence to the liver where it is converted into, and stored as, glycogen. It is stated (8) that a certain proportion of all carbohydrate ingested is attacked by the intestinal bacteria which split it up into the lower fatty acids and gases such as methane and carbon dioxide. Thus, even in the normal individual, a certain amount of glucose is definitely destroyed by the intestinal bacteria and does not reach the portal circulation.

Two curves are shown in Table II, whose general flat character and low peaks would appear to indicate that the absorption of glucose has not been occurring to anything like its normal extent. These curves are shown in detail in Table IV.

TABLE IV.

Case No.	Age.	Fasting.	Blood-sugar.				
			½ Hr.	1 Hr.	1½ Hrs.	2 Hrs.	2½ Hrs.
32	68	0·100	0·112	0·137	0·131	0·106	0·068
50	65	0·118	0·112	0·131	0·137	0·112	0·081

Curves of this type are due, in all probability, to deficient absorption of glucose. Several factors may cause this. In the first place, diminished motility of the stomach may delay the passage of the glucose into the small intestine, and so hinder absorption. Secondly, the intestinal mucosa may be so atrophied as to be incapable of absorbing glucose to the same extent as occurs in the normal young adult. Thirdly, a much larger amount of glucose may be destroyed by the intestinal bacteria than is destroyed in the normal young individual, and the amount of glucose remaining for absorption into the portal circulation may consequently be diminished.

V. *Curves Approximating to the Typical Diabetic Curve.*

In order to decide which curves should be included in this group it was necessary to lay down an arbitrary standard as to what should constitute a 'typical (mild) diabetic curve'. Curves were therefore included in this class whose peak values exceeded 0·24 per cent. and in which the blood-sugar had

not returned to its fasting level by the end of two and a half hours. Four such curves are present amongst those of the twenty-eight healthy people, and these are tabulated below.

TABLE V.

Case No.	Age.	Fasting.	Blood-sugar. ½ Hr.	1 Hr.	1½ Hrs.	2 Hrs.	2½ Hrs.	Sugar in Urine During Test.
14	81	0·106	0·181	0·250	0·293	0·275	0·168	Absent
18	72	0·100	0·218	0·293	0·262	0·218	0·175	Absent
35	69	0·075	0·181	0·268	0·237	0·175	0·131	Present
44	65	0·106	0·168	0·243	0·225	0·200	0·118	Present

If found in younger persons, curves such as these would be regarded as diagnostic of diabetes mellitus. Occurring as they do, however, in healthy old people who show no clinical signs whatever of the presence of this disease, they can only be regarded as indicative of the marked and symptomless disturbance of the carbohydrate mechanism which may occur in a certain proportion of aged people. Table II shows that the incidence of this type of curve is 14 per cent., and it is interesting to note that this figure is the same as that which has been determined for the frequency of the 'typical normal adult' type of curve in old age.

The Relationship of Disease to the Form of Sugar Tolerance Curve found.

A reference to Table I shows that, of the fifty cases investigated, there are twenty-two, to each of which a definite diagnosis could be assigned. In order to compare the curves of these cases with those of the healthy cases, they have been classified, and a table has been drawn up on the lines of Table II.

TABLE VI.

Type of Curve.	Case Numbers.	Incidence %.
Normal adult curve	21, 31, 44	14
Storage defect	3, 10, 26, 41, 40	23
'Lag' curve	4	4
'Flat' curve	2, 22	9
Typical diabetic curve	1, 6, 15, 23, 25, 27, 29, 30, 37, 43, 46	50

A comparison of these two tables is illuminating. It will be observed that the incidence of the 'normal adult' type of curve is the same in health and disease. The 'storage defect' type of curve occurs in 39 per cent. of the healthy cases, but in only 23 per cent. of the unhealthy cases. The 'lag' type occurs with less frequency in the unhealthy, the figures being 4 per cent. as against 25 per cent. The 'flat' curve is met with in 7 per cent. of the healthy cases and 9 per cent. of the diseased cases. Finally, the 'typical diabetic' type of curve shows a tremendous increase. Instead of the frequency of 14 per cent. which is present for healthy cases, the frequency of its occurrence in the unhealthy cases is found to be 50 per cent. This high figure accounts, of course, for the diminution in the incidence of the 'storage defect' type of curve which

has been noted. The reason for this increase is plain. The extra strain imposed on the carbohydrate mechanism by the presence of some disease converts, in many cases, the 'storage defect' curve of healthy old age into a 'diabetic' curve. A similar transformation also occurs in the case of the 'lag' type of curve.

The various diseases, noted in Table I, will now be considered individually.

Senility. Five subjects were examined who were definitely and grossly senile. Their curves are shown below:

Case No.	Age.	Fasting.	Blood-sugar.					Type of Curve.
			½ Hr.	1 Hr.	1½ Hrs.	2 Hrs.	2½ Hrs.	
4	73	0·093	0·187	0·293	0·131	0·112	—	Lag
6	74	0·093	0·125	0·250	0·300	0·193	0·162	Diabetic
15	65	0.112	0·281	0·268	0·231	0·168	0·143	Diabetic
22	94	0·131	0·118	0·131	0·100	0·118	0·112	Flat
37	72	0·118	0·150	0·243	0·250	0·181	0·143	Diabetic

It will be observed that three of the five curves are placed in the 'diabetic' category. This gives additional support to the conclusion that the carbohydrate mechanism becomes increasingly abnormal with advancing years. Case No. 22 is worthy of note. He was the oldest man of the series, and was in an advanced stage of senility. The curve found is of the 'flat' variety, and is evidently due to deficient absorption of the glucose feed. The probable reasons for this have already been advanced.

Chronic bronchitis. Five cases of severe chronic bronchitis are included. Of course, a considerable proportion of the cases examined showed some slight degree of emphysema and bronchitis, as was to be expected in patients of their age and type. The five mentioned, however, suffered from the condition to a marked degree, and their curves are shown below:

Case No.	Age.	Fasting.	Blood-sugar.					Type of Curve.
			½ Hr.	1 Hr.	1½ Hrs.	2 Hrs.	2½ Hrs.	
21	72	0·131	0·212	0·212	0·181	0·125	0·131	? Normal
23	83	0·100	0·143	0·212	0·243	0·200	0·162	Diabetic
25	76	0·106	0·168	0·256	0·268	0·275	0·181	Diabetic
27	73	0·187	0·262	0·349	0·312	0·293	0·225	Diabetic
46	71	0·125	0·175	0·206	0·193	0·237	0·193	Diabetic

The striking point about this group of cases is that four out of the five curves are of a very well-marked diabetic type. The small number, of course, makes it impossible to dogmatize, but it is suggested that chronic bronchitis, when of any degree of severity, exerts a very definite influence on the sugar tolerance of the aged person. Case No. 21 is of a somewhat nondescript type, which has been classified as normal because it more nearly approaches that than any of the other four types.

Cardiac disease. Three cases of cardiac disease are shown in Table I. Case No. 10 was one of aortic regurgitation, and an examination of the curve shows a high fasting blood-sugar and a peak of 0·193 per cent. at one hour. There is also a storage defect. Case No. 26 was suffering from mitral regurgitation, and the heart was much dilated. A soft systolic aortic bruit was also present. This case also shows a high fasting blood-sugar, and a peak of 0·181 per cent., sustained for half an hour, is present. A slight storage defect is observed. Case No. 34 was suffering from myocardial degeneration. No valvular lesion was detected, but the heart was dilated and the sounds were

feeble and indistinct. The patient had had repeated attacks of cardiac failure, which, however, had always responded to treatment by digitalis. A practically normal curve is present here.

The curves of these three cases show no abnormality which cannot be held to be attributable to the presence of old age alone, and the presence of heart disease appears to have exercised no appreciable effect on the character of the curves.

Rheumatoid arthritis. Two cases of advanced rheumatoid arthritis are included. Case No. 3 shows a storage defect and a high fasting blood-sugar (0·131 per cent.). The blood-sugar two and a half hours after glucose was 0·143 per cent., and no sugar appeared in the urine throughout. Case No. 43 shows a definite storage defect and a very high peak (0·243 per cent.); the blood-sugar two and a half hours after glucose was 0·131 per cent., and the curve is therefore placed in the 'diabetic' category in Table VI. Both these cases have curves which are somewhat abnormal in type, but as similar curves have been shown to occur with considerable frequency in perfectly healthy old people no specific responsibility can be attached to the presence of rheumatoid arthritis in their causation.

Chronic osteitis of tibia. One example of this condition is present (Case No. 1), and it is interesting to note the very abnormal type of curve found. There is a definite storage defect, and the peak of the curve is 0·281 per cent. No alteration in the renal threshold has occurred, as sugar was freely excreted in the urine once the blood-sugar had risen above the normal renal threshold. These changes can be attributed to the very marked septic focus present in the tibia.

Senile gangrene of foot. In the one case of this condition included (Case No. 2), an extremely low, 'flat' type of curve was elicited. This was probably due to deficient absorption of glucose, the reasons for which have already been considered.

Tuberculous neck sinuses. This case (No. 30) also shows the results produced by a marked septic focus, the sinuses being secondarily infected by pyogenic organisms. A curve of the diabetic type is present, and in spite of the height of the peak (0·25 per cent.) only a trace of sugar was present in the urine at one hour, and none subsequently. A high renal threshold is therefore present.

Carbuncle of back. This case (No. 31) is of some interest, because in spite of its possessing a very definite septic focus—a large carbuncle—the sugar tolerance curve is practically normal. Possibly the explanation of this may be found in the fact that the sepsis was of very recent origin.

Parenchymatous goitre. The one case of this condition present in the series showed no special points which might be ascribed to the goitre. The curve showed some defect in storage of glucose, and it took one and a half hours for it to reach its peak of 0·187 per cent. The blood-sugar two and a half hours after the glucose feed was 0·125 per cent.

Carcinoma. Two cases of carcinoma are included. Case No. 29 was one of carcinoma of the oesophagus which had not reached a very advanced stage. That is to say, swallowing was still possible with some degree of comfort, although a very obvious stricture of the oesophagus was found on radiological examination. The sugar curve in this case showed a well-marked storage defect. The high peak of 0·243 per cent. was reached in one and a half hours, and after two and a half hours the blood-sugar was still 0·175 per cent. Sugar was present in the urine in measurable quantities in the one-, two-, and four-hourly specimens. There is thus no difficulty in classifying this as a diabetic type of curve. Case No. 40 was one of carcinoma of the prostate. There was here a definite storage defect, as the blood-sugar two hours after glucose was still

0·156 per cent. Were it not for this fact one would be inclined to class this as a 'lag' curve, owing to the remarkable way in which the blood-sugar shoots up to its maximum of 0·293 per cent. in the first half-hour, and then as suddenly drops to 0·181 per cent. in the second half-hour of the test. Only a trace of sugar was present in the two-hour specimen of urine, and none at all in the other specimens. The renal threshold is therefore very high.

Both these cases show a derangement of the carbohydrate mechanism, although it is difficult to say whether this is due to the advanced age of the patients or to the malignant disease from which they were suffering. In view of similar findings in many cases of healthy old age, one is inclined to think that the malignant disease has taken little if any part in altering the appearance of the blood-sugar curves.

The Average Blood-sugar Curve in Elderly People.

The various types of blood-sugar curves which may be found in elderly people have been discussed, and the frequency with which these types occur in the series of cases investigated has been determined, both in health and disease. It was thought, however, that it would be useful to give some general indication of the form of curve which may be expected in this type of case. The twenty-eight healthy cases were therefore taken, and the corresponding blood-sugar readings of each case were added together and the resulting totals divided by the number of readings. Similar calculations were performed in the case of the twenty-two unhealthy cases. Two curves were thus produced, the first being the average curve of healthy old age, and the second being the average curve of old age complicated by the presence of some pathological condition. These curves are shown below.

Blood-sugar readings.

Fasting: 0·103 per cent.
½ hour: 0·172 „ „
1 hour: 0·209 „ „
1½ hours: 0·175 „ „
2 hours: 0·132 „ „
2½ hours: 0·099 „ „

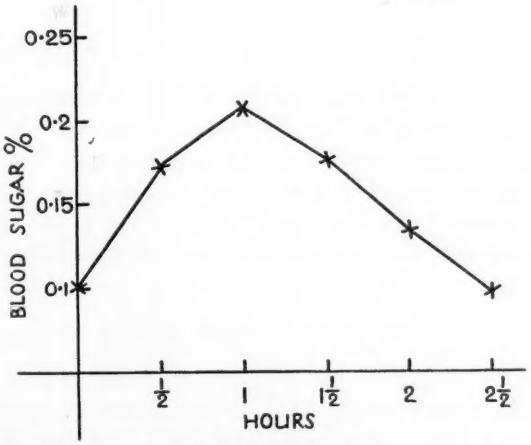

FIG. 1. Average blood-sugar curve in healthy old age.

It will be seen that, in the case of the curve for healthy old age, the fasting level is a little higher than the normal. The peak of 0·209 per cent. is high, and is reached at one hour instead of at half an hour, and at the end of two hours the blood-sugar is still 0·132 per cent., and a storage defect is therefore present.

At two and a half hours the blood-sugar has fallen to a little below its fasting level.

Blood-sugar readings.

Fasting: 0·109 per cent.
½ hour: 0·171 „ „
1 hour: 0·214 „ „
1½ hours: 0·208 „ „
2 hours: 0·172 „ „
2½ hours: 0·141 „ „

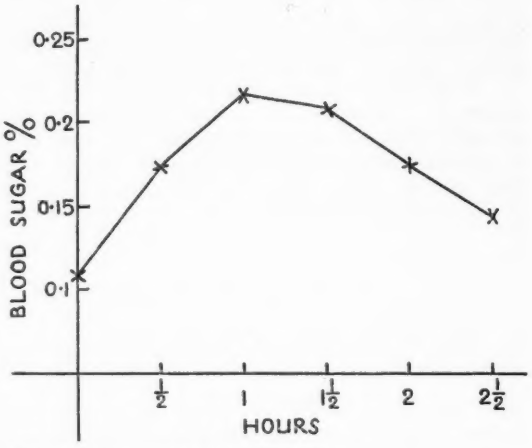

FIG. 2. Average blood-sugar curve in unhealthy old age.

The curve for unhealthy old age illustrates the pronounced influence which the presence of a pathological condition has upon the sugar tolerance of the aged. The fasting level is a little higher, as also is the peak which is reached at one hour. The fall is then much more gradual than in the case of the healthy subject, and at two and a half hours the blood-sugar is still 0·141 per cent. The storage defect is thus much greater, and the curve is tending towards the diabetic type.

The Blood-pressure and the Sugar-tolerance Curve.

In all the cases investigated the blood-pressure was estimated as a routine by means of a 'Tycos' sphygmomanometer. It was thought possible at the outset that some interesting facts might be brought to light when the results were correlated with the blood-sugar findings. This was not so, and no relation whatever has been traced between the height of the blood-pressure and the sugar-content of the blood or the renal threshold.

The Effect of a Septic Focus on the Sugar-tolerance Curve.

It is well known that any gross focus of sepsis in the body tends to diminish the sugar tolerance. In this series there are several cases in which the effects of a septic focus can be observed. Thus Case No. 1 (chronic osteitis of tibia) and Case No. 30 (infected tuberculous sinuses in the neck) are typical examples of the results of long-standing suppuration on the blood-sugar curve. Case No. 31 (carbuncle of back) showed a practically normal curve, but this, as has been suggested, is probably due to the sepsis being of very recent origin. These three cases are the only examples in the series of a gross septic focus.

The question of dental sepsis is interesting. Many of the subjects tested were edentulous, but of those possessing teeth nineteen showed well-marked dental sepsis. One would have expected this to have had some effect on the sugar-tolerance curve, but this was not so. Very high curves were certainly obtained in some cases, but similar curves were also present in many of the edentulous cases. Indeed, in eight of these nineteen cases of grossly septic teeth, no defect in the storage mechanism for glucose is apparent. One is thus brought to the conclusion that, in old age at any rate, dental sepsis of itself has little if any effect on the sugar tolerance.

The Renal Threshold in Old Age.

It has been established that the renal threshold for the normal young adult varies between 0·17 per cent. and 0·18 per cent. In the aged this level is found to be considerably raised in the majority of healthy subjects. The following tables help to demonstrate this, and they show, for each case, the blood-sugar concentration at the highest point of the curve and whether or not sugar appeared in the urine during the test.

TABLE VIII. *Healthy Cases.*

Case No.	Peak Value. %	Sugar in Urine.	Case No.	Peak Value. %	Sugar in Urine.
5	0·193	—	28	0·168	—
7	0·231	—	32	0·137	—
8	0·268	—	33	0·181	—
9	0·243	—	35	0·268	Trace
11	0·250	Trace	36	0·231	—
12	0·268	Yes	38	0·225	Yes
13	0·175	Yes	39	0·168	—
14	0·293	—	42	0·175	Trace
16	0·262	Trace	44	0·243	Yes
17	0·250	—	45	0·225	—
18	0·293	—	47	0·200	—
19	0·268	—	48	0·200	Yes
20	0·237	—	49	0·156	—
24	0·175	—	50	0·137	Trace

TABLE VIII. *Unhealthy Cases.*

Case No.	Peak Value. %	Sugar in Urine.	Case No.	Peak Value. %	Sugar in Urine.
1	0·281	Yes	26	0·181	—
2	0·131	—	27	0·349	Yes
3	0·181	—	29	0·243	Yes
4	0·293	Yes	30	0·250	Trace
6	0·300	Yes	31	0·156	—
10	0·193	Trace	34	0·181	—
15	0·281	Yes	37	0·250	Trace
21	0·212	—	40	0·293	Trace
22	0·131	—	41	0·187	—
23	0·243	Trace	43	0·243	Trace
25	0·275	Trace	46	0·237	—

Unfortunately, it is impossible to deduce with accuracy the level of the renal threshold in old age from the data available. To do this, it would have been necessary to estimate the blood-sugar and to test the urine at much more

frequent intervals than has been done. In this type of case specimens of urine are only obtained with great difficulty, and very frequent specimens, such as would have been required, are usually an impossibility.

A good deal of information is, however, obtainable from Tables VII and VIII. An examination of Table VII shows that eighteen of the twenty-eight healthy cases—that is, 64 per cent.—showed no glycosuria after the glucose feed. In spite of this, the peak values of these cases are consistently high, their average being 0·217 per cent. Of the remaining ten cases, five showed only a trace of sugar in the urine during the test, while in the urine of the other five sugar was present in measurable quantities.

On comparing these results with Table VIII it is found that, in the case of the twenty-two unhealthy subjects, there are only nine cases, or 40 per cent., in which glycosuria occurred.

It would appear, therefore, that in healthy old age the renal threshold is generally raised, probably to about 0·200 per cent. When some disease is present, however, glycosuria tends to occur with greater frequency. This is no doubt due, in part, to the greater frequency of the 'diabetic' type of curve in this class of case.

Conclusions.

1. Five types of glucose-tolerance curves occur in healthy old people. These are (1) the normal adult, (2) the storage defect, (3) the 'lag', (4) the 'flat', and (5) the typical diabetic types. The frequency with which each of these types occur has been indicated, and the storage-defect type has been shown to occur most frequently.

2. The 'lag' type of curve occurs in 25 per cent. of healthy cases, and this is probably a much higher incidence than is found in the normal adult.

3. The same five types of curve occur also in the group of unhealthy cases, but the incidence of each type is altered and the 'diabetic' type preponderates, and is found in as many as 50 per cent. of cases. It is concluded that the majority of diseases, when they occur in old age, have a deleterious effect on the sugar tolerance. This is particularly so in the case of chronic bronchitis.

4. Average curves are calculated (1) for healthy cases of old age, and (2) for unhealthy cases. These are compared.

5. No relation can be traced between the height of the blood-pressure, and either the sugar content of the blood, or the renal threshold.

6. Two cases are described in which the presence of a septic focus appears to have produced a diminution in the sugar tolerance. It is shown that dental sepsis of itself exerts little, if any, effect on the sugar-tolerance curve.

7. The renal threshold in healthy old age is generally raised, and may be taken to be in the neighbourhood of 0·200 per cent.

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APPENDIX.

Case 1. M. W.; aged 73; Miner. *Diagnosis*, Chronic osteitis of tibia; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, None; *Respiratory System*, Marked emphysema; *Heart*, Sounds very distant, otherwise normal; *Vessels*, No appreciable thickening; *Blood-pressure*, 170/90. There is a discharging sinus over the front of the lower third of the left tibia which has been present for several years. X-ray examination shows the presence of a sequestrum. *Urine* (*24-hour specimen*), *Amount*, 23 oz., *Specific Gravity*, 1020, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S. 0·068 per cent.	*Urine Sugar*, Absent.		
½ hour	„ 0·143 „			
1 „	„ 0·268 „	„	„	Present.
1½ „	„ 0·281 „			
2 „	„ 0·150 „	„	„	Present.
2½ „	„ 0·143 „			

Urine 4 hours after glucose, No sugar.

Case 2. E. O.; aged 69. *Diagnosis*, Senile gangrene of toes; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, None; *Respiratory System*, Normal; *Heart*, normal; *Vessels*, Thickened and calcareous; *Blood-pressure*, 130/95. This patient was suffering from gangrene of each great toe. The terminal phalanx in each case had sloughed off and had left a clean granulating surface. *Urine* (*24-hour specimen*), *Amount*, 45 oz., *Specific Gravity*, 1028, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S. 0·118 per cent.	*Urine Sugar*, Absent.		
½ hour	„ 0·112 „			
1 „	„ 0·131 „	„	„	Absent.
1½ „	„ 1·112 „			
2 „	„ 0·093 „	„	„	Absent.

Urine 4 hours after glucose, No sugar.

Case 3. O. M.; aged 70; Miner. *Diagnosis*, Rheumatoid Arthritis; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Three septic stumps remaining; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, Thickened and nodular; *Blood-pressure*, 150/110. This patient is suffering from advanced Rheumatoid Arthritis, with considerable deformity of the hands and feet. *Urine* (*24-hour specimen*), *Amount*, 40 oz., *Specific Gravity*, 1010, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·131	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·162	„			
1	„	0·175	„			
1½	„	—				
2	„	0·181	„			
2½	„	0·143	„	„	„	Absent.

Urine 4 hours after glucose, No sugar.

Case 4. J. H.; aged 73; Labourer. *Diagnosis*, Senility; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, One stump only remaining, no sepsis; *Respiratory System*, Emphysema present; *Heart*, Sounds rather distant, otherwise normal; *Vessels*, Thickened and tortuous, but not calcareous; *Blood-pressure*, 200/110. *Urine* (*24-hour specimen*), *Amount*, 48 oz., *Specific Gravity*, 1014, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·693	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·187	„			
1	„	0·293	„	„	„	Present.
1½	„	0·131	„			
2	„	0·112	„	„	„	Trace.

Urine 4 hours after glucose, No sugar.

Case 5. T. B.; aged 75; Labourer. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Constipation complained of; left inguinal hernia present; *Teeth*, Blackened and carious, well-marked pyorrhoea; *Respiratory System*, Emphysema; *Heart*, Normal; *Vessels*, No appreciable thickening; *Blood-pressure*, 185/80. *Urine* (*24-hour specimen*), *Amount*, 48 oz., *Specific Gravity*, 1012, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·137	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·106	„			
1	„	0·156	„	„	„	Absent.
1½	„	0·193	„			
2	„	0·175	„	„	„	Absent.
2½	„	0·131	„			

Urine 4 hours after glucose, No sugar.

Case 6. G. W.; aged 74; Market gardener. *Diagnosis*, Senility, some mental deterioration; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, One stump only remaining, no sepsis; *Respiratory System*, Slight emphysema; *Heart*, Sounds feeble, otherwise normal; *Vessels*, Markedly thickened but not calcareous; *Blood-pressure*, 180/100. *Urine* (*24-hour specimen*), *Amount*, 48 oz., *Specific Gravity*, 1010, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·093	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·125	„			
1	„	0·250	„	„	„	Trace.
1½	„	0·300	„			
2	„	0·193	„	„	„	Present.
2½	„	0·162	„			

Urine 4 hours after glucose, Trace of sugar present.

Case 7. E. H.; aged 73; Market gardener. *Diagnosis*, A healthy old man. This patient left the institution before a detailed clinical examination could be made.

Glucose Tolerance Test:

Fasting	B. S.	0·112	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·163	„			
1 „	„	0·231	„	„	„	Absent.
1½ „	„	0·175	„			
2 „	„	0·106	„	„	„	Absent.
2½ „	„	0·086	„			

Urine 4 hours after glucose, No sugar.

Case 8. J. H.; aged 69; Farm labourer. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Blackened and carious, but no gross sepsis; *Respiratory System*, Marked emphysema; *Heart*, Normal; *Vessels*, Thickened but not calcareous; *Blood-pressure*, 152/80; *Urine* (*24-hour specimen*), *Amount*, 46 oz., *Specific Gravity*, 1012, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·112	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·162	„			
1 „	„	0·268	„	„	„	Absent.
1½ „	„	0·237	„			
2 „	„	0·175	„	„	„	Absent.
2½ „	„	0·125	„			

Urine 4 hours after glucose, No sugar.

Case 9. D. C.; aged 79; Miner. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Two stumps remaining, no sepsis; *Respiratory System*, Emphysema; *Heart*, Normal; *Vessels*, No appreciable thickening; *Blood-pressure*, 165/110. *Urine* (*24-hour specimen*), *Amount*, 41 oz., *Specific Gravity*, 1010, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·081	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·118	„			
1 „	„	0·243	„	„	„	Absent.
1½ „	„	0·187	„			
2 „	„	0·137	„	„	„	Absent.
2½ „	„	0·125	„			

Urine 4 hours after glucose, No sugar.

Case *10.* W. K.; aged 74; Bricklayer's labourer. *Diagnosis*, Aortic regurgitation; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Grossly septic; *Respiratory System*, Emphysema; *Heart*, Aortic diastolic murmur; *Vessels*, Thickened, nodular, and calcareous; *Blood-pressure*, 224/96. This patient complained of pain down his right arm and at the back of his neck. *Urine* (*24-hour specimen*), *Amount*, 36 oz., *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·120	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·125	„			
1 „	„	0·193	„	„	„	Absent.
1½ „	„	0·172	„			
2 „	„	0·143	„	„	„	Absent.
2½ „	„	0·106	„			

Urine 4 hours after glucose, No sugar.

Case 11. C. D.; aged 67; Miner. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, About twelve septic stumps present; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, Thickened, nodular, and calcareous; *Blood-pressure*, 154/82; *Urine* (*24-hour specimen*), *Amount*, 31 oz., *Specific Gravity*, 1012, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S. 0·150 per cent.	*Urine Sugar*, Absent.		
½ hour	„ 0·175 „			
1 „	„ 0·250 „	„	„	Trace.
1½ „	„ 0·187 „			
2 „	„ 0·137 „	„	„	Absent.
2½ „	„ 0·100 „			

Urine 4 hours after glucose, No sugar.

Case 12. W. B.; aged 66; Hawker. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Marked pyorrhoea; *Respiratory System*, Slight emphysema; *Heart*, Normal; *Vessels*, Slight thickening, not calcareous; *Blood-pressure*, 170/104; *Urine* (*24-hour specimen*), *Amount*, 57 oz., *Specific Gravity*, 1010, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S. 0·100 per cent.	*Urine Sugar*, Absent.		
½ hour	„ 0·268 „			
1 „	„ 0·231 „	„	„	Present.
1½ „	„ 0·131 „			
2 „	„ 0·118 „	„	„	Trace.
2½ „	„ 0·106 „			

Urine 4 hours after glucose, No sugar.

Case 13. A. P.; aged 73; Labourer. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Remaining teeth show presence of pyorrhoea; *Respiratory System*, Emphysema; *Heart*, Normal; *Vessels*, Arteriosclerotic; *Blood-pressure*, 120/58; *Urine* (*24-hour specimen*), *Amount*, 48 oz., *Specific Gravity*, 1020, *Albumin*, Absent, *Sugar*, Trace.

Glucose Tolerance Test:

Fasting	B. S. 0·105 per cent.	*Urine Sugar*, Absent.		
½ hour	„ 0·125 „			
1 „	„ 0·175 „	„	„	0·26 per cent.
1½ „	„ 0·118 „			
2 „	„ 0·100 „	„	„	Absent.
2½ „	„ 0·081 „			

Urine 4 hours after glucose, No sugar.

Case 14. C. C.; aged 81; Miner. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Eight septic stumps remaining; *Respiratory System*, Marked emphysema; *Heart*, Rhythm irregular, no valvular lesions; *Vessels*, No appreciable thickening; *Blood-pressure*, 198/90; *Urine* (*24-hour specimen*), *Amount*, 32 oz., *Specific Gravity*, 1012, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S. 0·106 per cent.	*Urine Sugar*, Absent.		
½ hour	„ 0·081 „			
1 „	„ 0·250 „	„	„	Absent.
1½ „	„ 0·293 „			
2 „	„ 0·275 „	„	„	Absent.
2½ „	„ 0·168 „			

Urine 4 hours after glucose, No sugar.

Case 15. N. T.; aged 65; Waggoner. *Diagnosis,* Senility; *Clinical Examination*: *Alimentary System,* Normal; *Teeth,* None; *Respiratory System,* Normal; *Heart,* Normal; *Vessels,* No appreciable thickening; *Blood-pressure,* 180/90; *Urine* (*24-hour specimen*), *Amount,* 40 oz., *Specific Gravity,* 1010, *Albumin,* Absent, *Sugar,* Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·112	per cent.	*Urine Sugar,*	Absent.	
½ hour	„	0·281	„			
1 „	„	0·268	„			
1½ „	„	0·231	„			
2 „	„	0·168	„	„	„	0·25 per cent.
2½ „	„	0·143	„			

Urine 4 hours after glucose, No sugar.

Case 16. J. B.; aged 70; Labourer. *Diagnosis,* A healthy old man; *Clinical Examination*: *Alimentary System,* Normal; *Teeth,* None; *Respiratory System,* Emphysema; *Heart,* Normal; *Vessels,* Markedly thickened, tortuous and nodular; *Blood-Pressure,* 190/100.

Glucose Tolerance Test:

Fasting	B. S.	0·112	per cent.	*Urine Sugar,*	Absent.	
½ hour	„	0·262	„			
1 „	„	0·256	„	„	„	Trace.
1½ „	„	0·200	„			
2 „	„	0·143	„	„	„	Absent.
2½ „	„	0·100	„			

Urine 4 hours after glucose, No sugar.

Case 17. M. T.; aged 69; Vagrant. *Diagnosis,* A healthy old man; *Clinical Examination*: *Alimentary System,* Normal; *Teeth,* Six very septic stumps remaining; *Respiratory System,* Emphysema; *Heart,* Normal; *Vessels,* No appreciable thickening; *Blood-pressure,* 210/105. *Urine* (*24-hour specimen*), *Amount,* 24 oz., *Specific Gravity,* 1020, *Albumin,* Absent, *Sugar,* Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·112	per cent.	*Urine Sugar,*	Absent.	
½ hour	„	0·193	„			
1 „	„	0·250	„	„	„	Absent.
1½ „	„	0·181	„			
2 „	„	0·137	„	„	„	Absent.
2½ „	„	0·106	„			

Urine 4 hours after glucose, No sugar.

Case 18. J. B.; aged 72; Chef. *Diagnosis,* A healthy old man. This patient left the Institution before a detailed clinical examination could be made.

Glucose Tolerance Test:

Fasting	B. S.	0·100	per cent.	*Urine Sugar,*	Absent.	
½ hour	„	0·218	„			
1 „	„	0·293	„	„	„	Absent.
1½ „	„	0·262	„			
2 „	„	0·218	„	„	„	Absent.
2½ „	„	0·175	„			

Urine 4 hours after glucose, No sugar.

Case 19. W. B.; aged 69; Porter. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Five septic stumps; left inguinal hernia present; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, Normal; *Blood-pressure*, 120/70; *Urine (24-hour specimen)*, *Amount*, 36 oz., *Specific Gravity*, 1010, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·131	per cent.	*Urine Sugar*,	Absent.
½ hour	„	0·250	„		
1 „	„	0·268	„	„ „	Absent.
1½ „	„	0·237	„		
2 „	„	0·193	„	„ „	Absent.
2½ „	„	0·150	„		

Urine 4 hours after glucose, No sugar.

Case 20. P. G.; aged 66; Farm labourer. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Complains of constipation, nothing abnormal found on examination; *Teeth*, Five carious stumps present; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, Slight atheroma; *Blood-pressure*, 154/100; *Urine (24-hour specimen)*, *Amount* 40 oz., *Specific Gravity*, 1020, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test.

Fasting	B. S.	0·106	per cent.	*Urine Sugar*,	Absent.
½ hour	„	0·193	„		
1 „	„	0·237	„	„ „	Absent.
1½ „	„	0·125	„		
2 „	„	0·093	„	„ „	Absent.
2½ „	„	0·068	„		

Urine 4 hours after glucose, No sugar.

Case 21. J. P.; aged 72; Farm labourer. *Diagnosis*, Chronic bronchitis; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Eight septic stumps remaining; *Respiratory System*, Marked chronic bronchitis and emphysema; *Heart*, dilated, sounds weak, rhythm irregular; *Vessels*, Some nodular thickening; *Blood-pressure*, 160/100. This patient had a suprapubic prostatectomy performed three years ago, and there is now a large hernia through the scar. *Urine (24-hour specimen)*, *Amount*, 24 oz., *Specific Gravity*, 1024, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·131	per cent.	*Urine Sugar*,	Absent.
½ hour	„	0·212	„		
1 „	„	0·212	„	„ „	Absent.
1½ „	„	0·181	„		
2 „	„	0·125	„	„ „	Absent.
2½ „	„	0·131	„		

Urine 4 hours after glucose, No sugar.

Case 22. G. D.; aged 94; Shoemaker. *Diagnosis*, Senility. This patient was grossly senile, and died nine days after the glucose tolerance curve had been obtained. No opportunity was obtained for a detailed clinical examination.

Glucose Tolerance Test:

Fasting	B. S.	0·131	per cent.	*Urine Sugar*,	Absent.
½ hour	„	0·118	„	} No further specimens of urine were obtainable throughout the test.	
1 „	„	0·131	„		
1½ „	„	0·100	„		
2 „	„	0·118	„		
2½ „	„	0·112	„		

Case 23. G. S.; aged 83; Labourer. *Diagnosis*, Chronic bronchitis; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, None; *Respiratory System*, Very advanced chronic bronchitis; *Heart*, Sounds very feeble; *Vessels*, Slightly thickened; *Blood-pressure*, 145/70; *Urine* (*24-hour specimen*), *Amount*, 32 oz., *Specific Gravity*, 1015, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S. 0·100 per cent.	*Urine Sugar*, Absent.	
½ hour	„ 0·143 „		
1 „	„ 0·212 „	No specimen obtainable.	
1½ „	„ 0·243 „		
2 „	„ 0·200 „	*Urine Sugar*, Trace.	
2½ „	„ 0·162 „		

Urine 4 hours after glucose, No sugar.

Case 24. J. S.; aged 70; Seagoing engineer. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Two stumps present, no sepsis; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, No appreciable thickening; *Urine* (*24-hour specimen*), *Amount*, 45 oz., *Specific Gravity*, 1015, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S. 0·112 per cent.	*Urine Sugar*, Absent.	
½ hour	„ 0·175 „		
1 „	„ 0·168 „	„ „	Absent.
1½ „	„ 0·112 „		
2 „	„ 0·093 „	„ „	Absent.
2½ „	„ 0·086 „		

Urine 4 hours after glucose, No sugar.

Case 25. E. E.; aged 76; Brass finisher. *Diagnosis*, Chronic bronchitis; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, None; *Respiratory System*, Well-marked chronic bronchitis; *Heart*, Sounds feeble, organ dilated; *Vessels*, No thickening; *Blood-pressure*, 110/60; *Urine* (*24-hour specimen*), *Amount*, 40 oz., *Specific Gravity*, 1015, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S. 0·106 per cent.	*Urine Sugar*, Absent.	
½ hour	„ 0·168 „		
1 „	„ 0·256 „	„ „	Absent.
1½ „	„ 0·268 „		
2 „	„ 0·275 „	„ „	Trace.
2½ „	„ 0·181 „		

Urine 4 hours after glucose, No sugar.

Case 26. J. J.; aged 76; Stonebreaker. *Diagnosis*, Mitral regurgitation; *Clinical Examination*: *Alimentary System*, Long-standing constipation; *Teeth*, Three stumps present, no sepsis; *Respiratory System*, Emphysema; *Heart*, Apex beat fifth interspace (one inch outside nipple line), loud-blowing systolic mitral bruit, soft systolic aortic bruit; *Vessels*, Marked nodular thickening; *Blood-pressure*, 160/50; *Urine* (*24-hour specimen*), *Amount*, 43 oz., *Specific Gravity*, 1020, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S. 0·125 per cent.	*Urine Sugar*, Absent.	
½ hour	„ 0·162 „		
1 „	„ 0·181 „	„ „	Absent.
1½ „	„ 0·181 „		
2 „	„ 0·137 „	„ „	Absent.
2½ „	„ 0·100 „		

Urine 4 hours after glucose, No sugar.

Case 27. D. B.; aged 73; Labourer. *Diagnosis*, Chronic bronchitis; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Several septic stumps in lower jaw; *Respiratory System*, Marked chronic bronchitis; *Heart*, Slightly dilated; *Vessels*, Slight thickening; *Blood-pressure*, 125/65; *Urine* (*24-hour specimen*), *Amount*, 96 oz., *Specific Gravity*, 1015, *Albumin*, Absent, *Sugar*, 1·2 per cent.

Glucose Tolerance Test:

Fasting	B. S.	0·187	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·269	„			
1 „	„	0·349	„	„	„	0·59 per cent.
1½ „	„	0·312	„			
2 „	„	0·293	„	„	„	0·58 „
2½ „	„	0·225	„			

Urine 4 hours after glucose, Trace of sugar.

Case 28. A. H.; aged 74; Groom. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, None; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, No appreciable thickening; *Blood-pressure*, 150/82; *Urine* (*24-hour specimen*), *Amount*, 36 oz., *Specific Gravity*, 1020, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·086	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·162	„			
1 „	„	0·168	„			
1½ „	„	0·137	„			
2 „	„	0·118	„			

Urine 4 hours after glucose, No sugar.

Case 29. C. S.; aged 70; Labourer. *Diagnosis*, Carcinoma of oesophagus; *Clinical Examination*: *Alimentary System*, Well-marked pyorrhoea, complains of considerable difficulty in swallowing—due to a carcinoma of the oesophagus, the presence of which was proved by radiological examination; *Respiratory System*, Some emphysema, radiological examination showed involvement of the right lung in carcinomatous process; *Heart*, Normal; *Vessels*, Thickened and tortuous; *Blood-pressure*, 180/70; *Urine* (*24-hour specimen*), *Amount*, 22 oz., *Specific Gravity*, 1020, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·062	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·131	„			
1 „	„	0·187	„	„	„	0·85 per cent.
1½ „	„	0·243	„			
2 „	„	0·206	„	„	„	1·25 „
2½ „	„	0·175	„			

Urine 4 hours after glucose, 1·05 per cent. sugar.

Case 30. C. F.; aged 74; Miner. *Diagnosis*, Infected tuberculous sinuses in neck; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, No gross sepsis; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, No appreciable thickening; *Blood-pressure*, 120/70. There are several discharging sinuses on each side of the neck which have been present for some years. They originated in tuberculous cervical glands, which broke down and became infected. *Urine* (*24-hour specimen*), *Amount*, 40 oz., *Specific Gravity*, 1010, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·081	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·193	„			
1	„	0·250	„	„	„	Trace.
1½	„	0·218	„			
2	„	0·243	„	„	„	Absent.
2½	„	0·162	„			

Urine 4 hours after glucose, No sugar.

Case 31. E. H.; aged 76; Watchmaker. *Diagnosis*, Carbuncle of back; *Clinical Examination*: *Alimentary System*, Normal; no teeth; *Respiratory System*, Slight emphysema; *Heart*, Normal; *Vessels*, No appreciable thickening; *Blood-pressure*, 130/80. There is a large carbuncle about 3 inches in diameter in the centre of the back. At the time of the test the carbuncle was discharging freely. *Urine* (*24-hour specimen*), *Amount*, 36 oz., *Specific Gravity*, 1020, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·100	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·112	„			
1	„	0·156	„	„	„	Absent.
1½	„	0·131	„			
2	„	0·086	„	„	„	Absent.
2½	„	0·125	„			

Urine 4 hours after glucose, No sugar.

Case 32. W. T.; aged 68; Groom. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; five remaining teeth, no sepsis; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, No appreciable thickening; *Blood-pressure*, 190/90; *Urine* (*24-hour specimen*), *Amount*, 56 oz., *Specific Gravity*, 1008, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·100	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·112	„			
1	„	0·137	„	„	„	Absent.
1½	„	0·131	„			
2	„	0·106	„	„	„	Absent.
2½	„	0·068	„			

Urine 4 hours after glucose, No sugar.

Case 33. T. T.; aged 70; Labourer. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Marked pyorrhoea present; *Respiratory System*, Slight emphysema; *Heart*, Normal; *Vessels*, Slight thickening; *Blood-pressure*, 190/80; *Urine* (*24-hour specimen*), *Amount*, 72 oz., *Specific Gravity*, 1010, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·086	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·137	„			
1	„	0·181	„	„	„	Absent.
1½	„	0·143	„			
2	„	0·093	„	„	„	Absent.
2½	„	0·062	„			

Urine 4 hours after glucose, No sugar.

Case 34. H. L.; aged 68; Brickyard labourer. *Diagnosis,* Myocardial degeneration; *Clinical Examination*: *Alimentary System,* Normal; *Teeth,* Six septic stumps in jaw; *Respiratory System,* Slight emphysema present; *Heart,* Dilated, sounds very feeble, no valvular lesions; *Vessels,* well-marked nodular thickening; *Blood-pressure,* 145/80. This patient has had numerous attacks of cardiac failure, which have always responded to treatment by digitalis. *Urine (24-hour specimen), Amount,* 60 oz., *Specific Gravity,* 1010, *Albumin,* Absent, *Sugar,* Absent.

Glucose Tolerance Test:

Fasting	B. S. 0·093 per cent.	*Urine Sugar,* Absent.		
½ hour	„ 0·162 „			
1 „	„ 0·181 „	„	„	Absent.
1½ „	„ 0·137 „			
2 „	„ 0·100 „	„	„	Absent.
2½ „	„ 0·068 „			

Urine 4 hours after glucose, No sugar.

Case 35. G. R.; aged 69; Platelayer. *Diagnosis,* A healthy old man; *Clinical Examination*: *Alimentary System,* Normal; *Teeth,* One stump only remaining; *Respiratory System,* Slight emphysema; *Heart,* Normal; *Vessels,* Slight thickening; *Blood-pressure,* 130/75; *Urine (24-hour specimen), Amount,* 56 oz., *Specific Gravity,* 1010, *Albumin,* Absent, *Sugar,* Absent.

Glucose Tolerance Test:

Fasting	B. S. 0·075 per cent.	*Urine Sugar,* Absent.		
½ hour	„ 0·181 „			
1 „	„ 0·268 „	„	„	Trace.
1½ „	„ 0·237 „			
2 „	„ 0·175 „	„	„	Trace.
2½ „	„ 0·131 „			

Urine 4 hours after glucose, No sugar.

Case 36. M. S.; aged 77; Labourer. *Diagnosis,* A healthy old man; *Clinical Examination*: *Alimentary System,* Normal; *Teeth,* Eight very septic stumps; *Respiratory System,* Slight emphysema; *Heart,* Normal; *Vessels,* Thickened but not calcareous; *Blood-pressure,* 150/90; *Urine (24-hour specimen), Amount,* 38 oz., *Specific Gravity,* 1020, *Albumin,* Absent, *Sugar,* Absent.

Glucose Tolerance Test:

Fasting	B. S. 0·075 per cent.	*Urine Sugar,* Absent.		
½ hour	„ 0·231 „			
1 „	„ 0·162 „	„	„	Absent.
1½ „	„ 0·125 „			
2 „	„ 0·068 „	„	„	Absent.
2½ „	„ 0·050 „			

Urine 4 hours after glucose, No sugar.

Case 37. I. B.; aged 72; Labourer. *Diagnosis,* Senility; *Clinical Examination*: *Alimentary System,* Normal; *Teeth,* None; *Respiratory System,* Emphysema; *Heart,* Normal; *Vessels,* Thickened but not calcareous; *Blood-pressure,* 240/110; *Urine (24-hour specimen), Amount,* 48 oz., *Specific Gravity,* 1015, *Albumin,* Absent. *Sugar,* Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·118 per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·150 „			
1 „	„	0·243 „	„	„	Absent.
1½ „	„	0·250 „			
2 „	„	0·181 „	„	„	Trace.
2½ „	„	0·143 „			

Urine 4 hours after glucose, No sugar.

Case 38. D. K.; aged 68; Carter. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Two stumps only, no sepsis; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, No appreciable thickening; *Blood-pressure*, 123/70; *Urine* (*24-hour specimen*), *Amount*, 60 oz., *Specific Gravity*, 1020, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·112 per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·225 „			
1 „	„	0·212 „	„	„	0·4 per cent.
1½ „	„	0·137 „			
2 „	„	0·068 „	„	„	Trace.
2½ „	„	0·050 „			

Urine 4 hours after glucose, No sugar.

Case 39. J. W.; aged 75; Miner. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, None; *Respiratory System*, Emphysema; *Heart*, Normal; *Vessels*, Nodular and calcareous; *Blood-pressure*, 185/100; *Urine* (*24-hour specimen*), *Amount*, 32 oz., *Specific Gravity*, 1010, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·093 per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·150 „			
1 „	„	0·168 „	„	„	Absent.
1½ „	„	0·118 „			
2 „	„	0·075 „	„	„	Absent.
2½ „	„	0·075 „			

Urine 4 hours after glucose, No sugar.

Case 40. T. P.; aged 73; Miner. *Diagnosis*, Carcinoma of prostate; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Twelve septic stumps remaining; *Respiratory System*, Emphysema; *Heart*, Normal; *Vessels*, Slight thickening; *Blood-pressure*, 130/75. This patient is suffering from a carcinoma of the prostate, and is very cachectic. *Urine* (*24-hour specimen*), *Amount*, 48 oz., *Specific Gravity*, 1020, *Albumin*, Present, *Sugar*, Absent. Deposit of pus on standing.

Glucose Tolerance Test:

Fasting	B. S.	0·106 per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·293 „			
1 „	„	0·181 „	„	„	Absent.
1½ „	„	0·162 „			
2 „	„	0·156 „	„	„	Trace.
2½ „	„	0·112 „			

Urine 4 hours after glucose, No sugar.

Case 41. J. S.; aged 72; Miner. *Diagnosis*, Parenchymatous goitre; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, None; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, Slight atheroma; *Blood-pressure*, 170/95. This patient has suffered from a simple parenchymatous goitre for about twenty years. There is a general enlargement of the thyroid gland, and there is a small adenoma the size of a walnut present in the isthmus. *Urine* (*24-hour specimen*), *Amount*, 50 oz., *Specific Gravity*, 1010, *Albumin*, Trace, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·100	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·150	„			
1 „	„	0·175	„	„	„	Absent.
1½ „	„	0·187	„			
2 „	„	0·181	„	„	„	Absent.
2½ „	„	0·125	„			

Urine 4 hours after glucose, No sugar.

Case 42. H. D.; aged 77; Groom. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Very carious, well-marked pyorrhoea; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, Normal; *Blood-pressure*, 195/98. *Urine* (*24-hour specimen*), *Amount*, 43 oz., *Specific Gravity*, 1012, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·093	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·131	„			
1 „	„	0·168	„	„	„	Trace.
1½ „	„	0·175	„			
2 „	„	0·137	„	„	„	Absent.
2½ „	„	0·106	„			

Urine 4 hours after glucose, No sugar.

Case 43. J. G.; aged 77; Farm labourer. *Diagnosis*, Rheumatoid arthritis; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, A few carious and septic stumps remaining; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, No appreciable thickening; *Blood-pressure*, 175/90. This patient is suffering from well-marked rheumatoid arthritis. There is considerable deformity of the hands and feet, and permanent flexion of both knees. *Urine* (*24-hour specimen*), *Amount*, 60 oz., *Specific Gravity*, 1007, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·112	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·193	„			
1 „	„	0·206	„	„	„	Absent.
1½ „	„	0·243	„			
2 „	„	0·218	„	„	„	Trace.
2½ „	„	0·131	„			

Urine 4 hours after glucose, No sugar.

Case 44. H. R.; aged 65; Farm labourer. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*; Complains of chronic indigestion, nothing abnormal found on examination; fairly good teeth, no sepsis; *Respiratory System*, Emphysema; *Heart*, Normal; *Vessels*, Normal; *Blood-pressure*, 115/70; *Urine* (*24-hour specimen*), *Amount*, 53 oz., *Specific Gravity*, 1010, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·106 per cent.	*Urine Sugar*,	Trace.	
½ hour	„	0·168 „			
1 „	„	0·243 „	„	„	1·25 per cent.
1½ „	„	0·225 „			
2 „	„	0·200 „	„	„	1·35 „
2½ „	„	0·118 „			

Urine 4 hours after glucose, 0·4 per cent. sugar.

Case 45. W. M.; aged 68; Miner. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Two stumps remaining, no sepsis; *Respiratory System*; Slight emphysema; *Heart*, Normal; *Vessels*, No appreciable thickening; *Blood-pressure*, 140/90. *Urine* (*24-hour specimen*), *Amount*, 36 oz., *Specific Gravity*, 1010, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·137 per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·143 „			
1 „	„	0·225 „	„	„	Absent.
1½ „	„	0·150 „			
2 „	„	0·112 „	„	„	Absent.
2½ „	„	0·075 „			

Urine 4 hours after glucose, No sugar.

Case 46. T. D.; aged 71; Miner. *Diagnosis*, Chronic bronchitis; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, None; *Respiratory System*, Well-marked chronic bronchitis and emphysema present; *Heart*, Dilated; *Vessels*, No appreciable thickening; *Blood-pressure*, 130/75; *Urine* (*24-hour specimen*), *Amount*, 34 oz., *Specific Gravity*, 1020, *Albumin*, Absent, *Sugar*, *Absent*.

Glucose Tolerance Test:

Fasting	B. S.	0·125 per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·175 „			
1 „	„	0·206 „	„	„	Absent.
1½ „	„	0·193 „			
2 „	„	0·237 „	„	„	Absent.
2½ „	„	0·193			

Urine 4 hours after glucose, No sugar.

Case 47. J. M.; aged 75; Labourer. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, None; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, slight thickening; *Blood-pressure*, 190/100; *Urine* (*24-hour specimen*), *Amount*, 24 oz., *Specific Gravity*, 1015, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·106 per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·200 „			
1 „	„	0·187 „	„	„	Absent.
1½ „	„	0·200 „			
2 „	„	0·131 „	„	„	Absent.
2½ „	„	0·100 „			

Urine 4 hours after glucose, No sugar.

Case 48. H. G.; aged 74; Railway shunter. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Very carious, no gross sepsis; *Respiratory System*, Normal; *Heart*, Sounds rather feeble, otherwise normal; *Vessels*, Normal; *Blood-pressure*, 150/80; *Urine* (*24-hour specimen*), *Amount*, 24 oz., *Specific Gravity*, 1020, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·118	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·156	„			
1 „	„	0·193	„	„	„	0·37 per cent.
1½ „	„	0·200	„			
2 „	„	0·081	„	„	„	Trace.
2½ „	„	0·075	„			

Urine 4 hours after glucose, No sugar.

Case 49. J. S.; aged 73; Scaffolder. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Six septic stumps remaining; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, Slight uniform thickening; *Blood-pressure*, 149/78; *Urine* (*24-hour specimen*), *Amount*, 30 oz., *Specific Gravity*, 1020, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·100	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·131	„			
1 „	„	0·143	„	„	„	Absent.
1½ „	„	0·156	„			
2 „	„	0·118	„	„	„	Absent.
2½ „	„	0·075	„			

Urine 4 hours after glucose, No sugar.

Case 50. G. B.; aged 65; Hawker. *Diagnosis*, A healthy old man; *Clinical Examination*: *Alimentary System*, Normal; *Teeth*, Good; *Respiratory System*, Normal; *Heart*, Normal; *Vessels*, Normal; *Blood-pressure*, 160/80; *Urine* (*24-hour specimen*), *Amount*, 44 oz, *Specific Gravity*, 1010, *Albumin*, Absent, *Sugar*, Absent.

Glucose Tolerance Test:

Fasting	B. S.	0·118	per cent.	*Urine Sugar*,	Absent.	
½ hour	„	0·112	„			
1 „	„	0·131	„	„	„	Trace.
1½ „	„	0·137	„			
2 „	„	0·112	„	„	„	Trace.
2½ „	„	0·081	„			

Urine 4 hours after glucose, No sugar.

616.155.2

THE BLOOD-PLATELET: ITS CLINICAL SIGNIFICANCE[1]

By W. MACKAY

This paper is based on a review of the available literature dealing with blood-platelets in conjunction with examination of the blood which I have made in a series of six healthy people and seventy-four patients. [Every paper mentioned in the bibliography has been personally consulted and I am responsible for all the platelet counts, amounting to about 820 in number. I am responsible also for the observations on platelet morphology and clot retraction and for frequent estimations of coagulation time and bleeding time, all of which were made at the time of the platelet count.]

Technique.

The following solution and apparatus were used both for the morphology and the enumeration of platelets:

(*a*) *Platelet diluting fluid.* 2 per cent. solution of sodium citrate made up in 0·29 per cent. solution of sodium chloride. Before use the fluid was heated to boiling point, filtered, and cooled.

(*b*) *Platinum wire loop*, 1/8 inch in diameter, coated with clean hard paraffin.

(*c*) *Straight Hagedorn needle.*

(*d*) *Clean blood slide*, on which a drop of a saturated solution of brilliant cresyl blue in absolute alcohol was first placed. The alcohol was then allowed to evaporate, and a thin film of precipitated stain was thus deposited on the slide.

(*e*) *Clean No. 1 cover slip*, 7/8 inch square.

The skin over the pulp of a finger was cleansed with absolute alcohol and allowed to dry. A drop of diluting fluid was then placed on the skin and the skin sharply punctured through the drop. The outflowing blood was allowed to pass directly into the diluting fluid. No pressure was used to make the blood flow freely. Care was taken to ensure that the blood was diluted in such a way that not more than 60 red corpuscles were present in any one microscopic field. In practice the number of erythrocytes present was usually in the neighbourhood of 40 per field. The blood and diluting fluids were thoroughly mixed together by means of the paraffined loop and a loopful of the mixture

[1] Received January 6, 1931.

transferred to the centre of the film of precipitated brilliant cresyl blue on the blood slide. It was then covered with the coverslip and ringed with vaseline. The amount of diluted blood transferred to the slide was such that the fluid spread out in a capillary layer between slide and coverslip. Two preparations were made and both were laid aside for at least 30 minutes at laboratory temperature to allow the blood elements to settle. During this period the number of red and white cells in the blood were enumerated in the usual way.

All the observation was done under oil immersion (objective 1/12 inch, eyepiece No. 4). For counting purposes the microscopic field was divided into quadrants. This was conveniently done by cutting out two cardboard rings of suitable size and gumming them together after two fine hairs stretched at right angles to each other had been placed between them. The whole arrangement was then inserted into the eyepiece.

Any preparation in which agglutination of platelets had occurred was discarded. The ratio of platelets to erythrocytes was determined in a series of successive fields, a total of at least 1,000 red cells being counted in each of *two* preparations. The average number of platelets per 1,000 erythrocytes was then determined from the results obtained from each preparation, and from the previously calculated number of red cells the number of platelets per cubic millimetre was obtained.

As a rule 100 platelets were examined and the size, granulation, and staining reaction of each recorded. The totals obtained were then tabulated in percentages. In those cases in which a marked thrombocytopenia existed as many platelets as could be found within a period of approximately 30 minutes were investigated. In the case of acute myeloblastic leukaemia the total number counted on two occasions was only two.

Coagulation Time.

The method used was that described by Gibbs (98). It consisted essentially in measuring the time taken by a drop of shed blood, obtained by puncture of the skin, to coagulate while it was kept moving to and fro on a loop of platinum wire. The end-point was definite and it was reached when the drop of blood ceased to move on the platinum loop. The coagulation time was estimated at a temperature which varied between 37° and 40° C. According to Gibbs the normal coagulation time at this temperature falls between 92 and 103 seconds. These figures are rather low, as it was found on many occasions that the coagulation time was as high as 150 seconds in patients whose blood, when examined by other methods, clotted within normal time limits. It may be that the blood used has been in contact with tissue juice and that it is difficult to control the amount of tissue fluid in any one drop of blood even where the greatest care is taken to avoid congestion in the capillary vessels of the skin when the puncture is made. Because of this difficulty the results obtained by Gibbs' method are not so reliable as those obtained by using

blood which has been taken from a vein with only a minimum of contact with the tissue fluids. The method has the advantage that it can be used to make daily estimations of coagulation time without great inconvenience to the patient. In the hands of the same individual the margin of error is reduced to a minimum. In this work the coagulation time of blood was regarded as prolonged or increased if it exceeded 150 seconds.

For the estimation of *clot retraction* clean capillary tubes, 4 or 5 inches long, were flamed until they were red hot and then allowed to cool. Blood obtained by needle puncture of the skin was drawn into the capillary tube until it was half full. After ensuring that the blood occupied the middle two-fourths of the tube it was set aside for 20 to 24 hours. (Sometimes the ends of the tube were sealed off in a Bunsen flame.) At the end of that time the amount of retraction and extrusion of serum was noted as being 'nil', 'poor', 'fair', or 'good'. In order to avoid the fallacy of asyneresis due to adhesion of the plasma to the walls of the tube care was taken in those cases in which retraction was 'nil' or 'poor' to tap each end of the capillary tube smartly on a glass slab in order to loosen the clot. The tube was then laid aside for further inspection to find out if loosening the clot had made any difference to the amount of retraction.

For estimation of the *bleeding time*, after the usual aseptic precautions the skin was punctured with a sharp Hagedorn needle to a depth of 3 to 4 mm. and the blood which flowed from the wound wiped away every 15 to 30 seconds by means of a piece of filter paper. Care was taken not to touch the edges of the wound. The time which elapsed between the commencement and cessation of the bleeding was noted as bleeding time. The site usually chosen for the puncture was the lobe of the ear. Occasionally the pulp of the thumb was used.

To test *capillary resistance*, the armlet of a mercurial sphygmomanometer was applied to the arm or leg in the usual way and the pressure raised to a point midway between systolic and diastolic blood-pressure. The pressure was maintained for a period of five minutes, after which the apparatus was removed and a search made for petechial haemorrhages.

Historical.

The earliest observers of mammalian blood-platelets seem to have been Donné[2] and Arnold,[2] both of whom described them about the middle of last century. Donné called them 'globulins'. Some thirty years later Hayem gave them the name 'hématoblastes'. It is to Bizzozero (43) that we owe the name 'blood-platelets'. Other writers have used the term 'thrombocytes' to describe platelets.

The existence of the platelet as a third morphological element of the circulating blood has been repeatedly affirmed and denied. Buckmaster (52)

[2] Cited from Degkwitz (72).

and Mathews (157) believe that the blood-platelet is merely a precipitate formed in altered blood-plasma, and Marino (156) failed to observe platelets in blood which was allowed to flow directly into absolute alcohol.

Downey (76), however, observed that 100 per cent. alcohol really distorted the platelets and rendered them difficult to demonstrate. Roskam (195) showed also that particles of precipitated plasma bore no resemblance to blood-platelets in size, shape, refraction, and staining reaction. Bedson (30) reported that the specific behaviour of precipitating (anti-serum) serum and of anti-fibrinogen serum had no action on the blood-platelets, while anti-platelet serum produced a diminution in the number of circulating platelets (thrombocytopenia). Bizzozero (43) described the platelets in life as they appeared in the mesenteric vessels of rabbits and guinea-pigs, and his observations have been confirmed by others, notably by Eberth and Schimmerbusch (84). They are also present in the blood of all mammals in numbers which are constant within limits, and in health and disease I have found them to fluctuate independently of the red and white cells.

It is now almost universally accepted that the platelet is a constant performed element in normal healthy blood.

Platelet Morphology in Health.

In shed blood the platelet rapidly loses its form and shape, and in order to keep it morphologically intact it is necessary to examine it in suspension in suitable media.

In health the platelet varies somewhat in size, stated by different authors to be from 2 to 3 microns (72) or from 2 to 5 microns (187) in diameter. I found the average normal diameter to vary between 2 and 3 microns. Larger or smaller platelets were very uncommon.

In wet preparations the blood-platelet is disk-like, and spherical or oval in shape, but at ordinary room temperatures the outline may sometimes become irregular, the cytoplasm being prolonged into spike-shaped processes of differing lengths and numbers arranged in a radial manner around the platelet. Occasionally the free end of these processes becomes enlarged and spherical, the platelet then being surrounded by knob-like or club-shaped projections. The appearance thus becomes that of a granular main body connected to these non-granular cytoplasmic masses by thin lines of cytoplasm. Such bizarre forms are only seen in wet preparations, and they may be regarded as artifacts. On a dry-blood film elongated forms may be observed.

The granules contained within the cytoplasm may be scattered uniformly throughout the cytoplasm or may be collected together in the centre or at the periphery of the platelet. Under normal conditions the number of granules varies within rather wide limits. Fegler (87) found that 60 to 70 per cent. of the platelets were ' rich ' in granules, while Reimann's figures (187) were 29 to

46 per cent. Both authors agreed that the larger the platelet the fewer were the granules it contained.

The question whether the platelet has a nucleus is one which a number of observers have attempted to answer. The so-called homologue of the platelet—the 'thrombocyte', 'spindle cell', or 'explosive corpuscle' of non-mammals—is nucleated.[3] With regard to the mammalian platelet Aynaud (22) thought that the cytoplasm contained nuclear substance in a diffuse state, and Herwerden (117) satisfied himself that all grades of transition from small pyknotic to large pale nuclei could be observed. He was never able to distinguish mitotic division. Prevailing opinion[4] favours the conception of the platelet as a non-nucleated element. Downey (76) stated that there was nothing in the staining reaction to show that the platelet was related to the nucleus of red or white cells. My observations support the idea that the nucleated appearance assumed by many platelets appeared to be due to the aggregation of the granules within the cytoplasm to form a rather dense mass. Nothing resembling a nuclear membrane was seen and mitosis was never observed.

Accordingly the platelet in health may be defined as a non-nucleated round or oval disk-like body, with an average diameter varying between 2 and 3 microns, and with a hyaline cytoplasm containing numerous granules.

Origin of Blood-platelets.

Many theories have been advanced to explain the origin of the blood-platelet, and at one time or another almost every cell belonging to, or derived from, the blood-forming tissues has been suspected of giving birth to the platelet. At present the consensus of opinion favours the idea that it is derived from the megakaryocyte of the bone-marrow, but it cannot be said that the problem is finally solved.

Hayem considered the blood-platelet to be the precursor of the red corpuscle. It has also been thought that the red cells by a process of budding or extrusion from their cytoplasm (49), and the leucocytes, by fragmentation of their cytoplasm, gave rise to platelets. A series of red cell, white cell, and platelet counts was made on each patient over periods varying from two weeks to two months. The results showed that there was no exact parallelism between the curves of the platelets and the red cells on the one hand, and those of the platelets and the white cells on the other, and that the platelets could vary numerically quite irrespective of numerical change in the totals of the other formed elements of the blood. Thus there is clinical evidence to show that the platelet is not directly related to either the red corpuscles or the white cells and is unlikely to be derived from them.

There is also some experimental evidence to support this view.[5] If the platelets were derived from the red or white corpuscles the anti-serum prepared

[3] References 2, 23, 43, 184, 185, 208, 209, 210, 212, and 213.

[4] References 43, 72, and 76.

[5] References 33, 34, 36, 64, and 138.

against these cells would produce a diminution in the number of circulating platelets. This has not been found to be the case, as such diminution can be induced only by injecting, not anti-red or anti-white cell sera, but anti-platelet serum. Further, Bedson and Johnston (36) on injecting anti-sera prepared against lymph glands and reticulo-endothelial cells could find no proof that the platelet derived its origin from these tissues.

The conception that the platelet is derived from the megakaryocyte of the bone-marrow was first formulated by Wright (223), and his work has been confirmed and consolidated by others (59, 76). Aschoff (17) considers the question settled beyond doubt.

In the embryo the megakaryocyte is found in the liver, spleen, and yolk-sac, while in the adult it is normally present only in the bone-marrow. In pathological states it has been observed however in the lungs, spleen, and blood-stream. In the bone-marrow it is present in all stages of development. The youngest form of the cell is non-granular and has a single nucleus which in the course of maturation becomes larger and more complex until ultimately several nuclei are formed.[6] The cytoplasm also increases in size and becomes full of very fine granules which Wright (223) and Downey (76) considered peculiar to the megakaryocyte and the blood-platelet. Thus the fully developed cell is very large and has a granular cytoplasm containing a number of nuclei. It is only in this adult state that the megakaryocyte can produce blood-platelets.[7]

In his classical work Wright (223) demonstrated that blood-platelets were portions of megakaryocytic cytoplasm which, after segmentation, were detached and carried off into the blood-stream. The cytoplasm was first prolonged into pseudopodia-like processes which projected into the blood channels through small openings in the vessel walls. Many of the granules seen in the megakaryocytic cytoplasm passed into the pseudopodia or collected into groups at the edge of the cell before segmentation occurred.

In support of this conception of platelet origin Wright, and subsequently others, pointed out the parallelism which existed between the number of blood-platelets in the circulation and the number of megakaryocytes in the bone-marrow. Both are increased in regenerative states following on haemorrhage and toxaemia, in inflammatory states, in myelogenous leukaemia (223), in Hodgkin's disease,[8] in experimental conditions following injections of anti-platelet serum (144) and anti-red cell serum (36), and following inoculation with diphtheria toxin (80). Both are diminished in pernicious anaemia and lymphatic leukaemia (223), in chronic benzol poisoning (202), in aleukia and aleukaemic leukaemia, (96, 97), and after exposure to X-rays (164). In favour of his hypothesis Wright also pointed out that the platelets did not appear in the embryo before the appearance of megakaryocytes or their forerunners and that they were found only in mammals in which the megakaryocyte was present.

In the realm of experiment Firket (91) produced thrombocytopenia in

[6] References 60, 92, 160, and 199.

[7] References 36, 92, and 223.

[8] References 59, 60, 204, and 223.

rabbits and then found that megakaryocytes appeared in the spleen. Within a few days there was an increase in the number of blood-platelets. In a splenectomized rabbit he found myeloid metaplasia in the liver, and in the lymphatic glands megakaryocytes were the sole myeloid elements present. Firket regarded his findings as supporting Wright's theory, but he was doubtful if the platelet arose solely from the megakaryocyte.

More direct proof is provided by the observation of Sabin (199), who watched the clumping of granules and fragmentation of the cytoplasm into typical platelets in megakaryocytes found in the circulation. Bedson and Johnston (36) examined megakaryocytes of the bone-marrow in a vital preparation, and they too observed the accumulation of granules into little masses about the size of the platelet. In some instances small platelet-like portions of the cytoplasm became attached to the periphery of the cell by a narrow stalk until ultimately the cytoplasm of these cells had become almost completely fragmented into small, irregular, oval and granular masses lying free in the surrounding medium. Commenting on these findings Bedson and Johnston thought that the megakaryocytes were undergoing degenerative changes rather than being in the active process of platelet production. After injecting anti-platelet serum they saw no megakaryocytes in process of active platelet budding although they noted that this serum produced an increase in the number of megakaryocytes in the bone-marrow. While their work may be considered as supporting Wright's theory these writers concluded that the relationship between megakaryocytic hyperplasia and increased platelet production was not clear. They appeared to be satisfied however that the platelet normally had its origin in the bone-marrow. In support of this conclusion they stated that anti-bone-marrow serum produced thrombocytopenia.

Less convincing evidence in support of Wright's conception is forthcoming from the work of Le Sourd and Pagniez (143, 144), who found that megakaryocytes brought about retraction of the blood clot. Thus because of the common retractile property existing between platelet and megakaryocyte they concluded that there was some close genetic relationship between the two elements.

McGowan (158) regarded the megakaryocyte as forming a reserve for the production of haematoblasts, and he suggested that blood-platelets might arise from the clippings and remnants formed by unequal division of haemoblasts.

With regard to the granules found in the megakaryocyte Woodcock (222) stated that they represented the unassimilable materials of red cells ingested by the megakaryocyte. Others (36, 93), however, have never seen red corpuscles within this cell and doubt if it has any phagocytic function. Downey (76) suggested that the granules characteristic of the megakaryocyte developed along with degenerative changes in the nucleus, and he further stated that the hyaline bodies which were constricted off from the cytoplasm of mononuclear cells and lymphocytes, especially in the rabbit, were in no way related to blood-platelets although they occasionally contained an azurophil granule. These azurophil granules were not, according to Downey, the same granules as were

found in the blood-platelet. This is of interest as some writers (50, 58) have suggested that in times of need there may be a reversion to a vicarious type of blood-platelet formation in which the large lymphocyte, the endothelial cells of the bone-marrow and the blood-vessels (66), the mononuclear and transitional cells of the bone-marrow, spleen, and blood may take on the task of platelet production.

From the foregoing considerations it will be evident that the platelet does not arise from the erythrocyte or leucocyte. There is very good evidence that it has its origin from the megakaryocyte. While that is so it cannot be claimed that the problem is solved beyond question. The fact that most of the evidence is based on morphological and tinctorial observations is unsatisfactory, and as a result there is uncertainty on the part of some investigators who, while they guardedly support the megakaryocytic origin, do not seem to be convinced that it is the sole mechanism of platelet genesis. However, it would seem reasonable to conclude that, in the adult, the platelet under normal conditions has its independent origin in the bone-marrow, and further, not unreasonable to assume that in times of stress it may arise from other tissues which are potentially haemopoietic.

Viability of the Blood-platelet.

The question as to whether the blood-platelet is a living element has given rise to a certain amount of speculation and research. The problem is not yet solved. Achard and Aynaud (3) noted that alteration in the form of the platelet was modified by change in temperature and by protoplasmic poisons such as ether, chloroform. quinine, and potassium cyanide. They noted further that under suitable conditions the platelets could decolorize dilute methylene blue solution, the colour reappearing however when the suspension was shaken (6). They observed also that the platelet could absorb neutral red, the dye being taken into the interior of the element (8). The ability to decolorize or absorb was abolished or modified by thermal changes, by the addition of sodium fluoride to the solution, and, in the case of methylene blue, by quinine. Although they never observed true amoeboid movement or division or multiplication of platelets Achard and Aynaud suggested that the motility, the ability to bring about alteration in form, and the properties of decolorization and absorption shown by the platelets, all of which phenomena could be modified or abolished by agents which inhibit or destroy vital activity, argued in favour of the viability of these elements.

Warburg's work (215) suggests that platelets can respire oxygen. In spite of this, proof of metabolic activity within the platelet is not very convincing, Roskam (195) thinks it necessary to find the respiratory quotient before the viability of the platelet can be definitely established.

Destruction of Blood-platelets.

In health the spleen constantly contains a large number of platelets and in disease it has been found to contain a relatively large number of these elements when their numbers were diminished in the circulating blood (124, 141). The platelets may be seen in the splenic sinuses, and their presence in the spleen may also be detected if a portion of that organ is teased out in a suitable medium and appropriately stained (32, 36). It seems to be assumed that the platelets are held up in the splenic sinuses preparatory to being destroyed. As proof of the destructive action of the spleen it has been shown that there is an increase in the number of platelets circulating in the blood after splenectomy, whether experimental (32, 36) or therapeutic. The same phenomenon has also been reported on ligature of the splenic artery (102). Further, it has been observed that the blood of the cubital vein and the splenic artery contains more platelets than the blood of the splenic vein (56, 166).

While these observations may be taken as suggestive evidence of the platelet-destroying function of the spleen yet it should be noted that an increase in the platelet count follows other operative procedures, whether experimental or therapeutic.[9] Moreover, increase in the number of circulating platelets does not always follow on splenectomy (47, 203). It is well known that the spleen acts as a reservoir for red corpuscles (27, 28), and it is likely that the platelets observed in the spleen are not retained solely for destruction but simply for storage purposes. There is some evidence to show that during acute asphyxia in dogs the platelets are mobilized, a phenomenon which does not occur after these animals are splenectomized (41). Further, after the administration of ephedrine (40) and adrenalin (42), both substances which bring about splenic contraction, there is a rise in the number of circulating platelets.

More convincing evidence in favour of the platelet-destroying function of the spleen would be afforded by the direct observation of intracellular destruction of these elements. Some workers[10] claim to have observed the presence of phagocytosed and degenerated platelets within the endothelial cells of the spleen. Kaznelson (124) thought that the platelets were lysed rather than phagocytosed, but he noted phagocytosis of platelets in the spleen of one case of pernicious anaemia. On the other hand Pardi (170), even where he saw what resembled blood-platelets within the phagocytic cells, was not satisfied that this was good evidence of phagocytosis.

Although the evidence for direct phagocytosis of platelets is contradictory it is likely that the platelets are destroyed by the phagocytic cells of the spleen. These cells belong to the reticulo-endothelial system, and it is interesting to find that when their function is inhibited by 'blocking' (32, 127) there is an increase in the number of platelets in the circulation. If splenectomy now be performed there is no further increase in the platelet count. However the

[9] References 24, 32, 35, 36, and 149.

[10] References 14, 65, and 201.

'blockade' is only temporarily effective. It may be that other tissues take over the function of platelet destruction or that the blockading substances produce a transient activity in the platelet-forming tissues.

Numerical Variations of Platelets in Health.

The adhesiveness of platelets for water 'wettable' surfaces and the ease with which they disintegrate outside the body make it very difficult to estimate the numbers in the circulation. This is reflected in the many methods which have been devised to count the platelets. It is not surprising, therefore, that the normal figure of each method differs. The following table illustrates the differences in the normal count according to the method used:

Average normal number of platelets per cm.	Author(s).
216,000	Aynaud (20)
250,000	Wright [11]
262,000 (skin puncture)	Buckman and Hallisey (51)
284,000 (venepuncture)	Gram (112)
Rarely less than 300,000	Thomsen [12]
350,000	Pratt [11]
450,000	

Platelets per c.mm. Normal limits.	Author(s).
150,000 to 300,000	Fonio [11]
183,000 to 252,000	Aynaud (20)
250,000 to 400,000	Cramer and Bannermann (66)
263,000 to 360,000	Degkwitz (72)

As the result of counting the platelets in six healthy subjects I found that the numbers varied not only with the individual but also in the same individual on the same and on different dates. In one case the variation in the count at different times during the same day was as much as 200,000 without any apparent cause. The average of 30 counts on these healthy subjects was 392,400 per c.mm., the counts ranging from 250,000 to 450,000. From these figures it is apparent that the platelet numbers fluctuate in health within a wide range, and it is evident that the fixing of a normal figure is at best only a rough guide to what constitutes the normal by the method of counting adopted. For the purposes of this investigation the average number of platelets per c.mm. of blood was fixed at 390,000, and counts falling between 250,000 and 450,000 per c.mm. were regarded as being within normal limits.

With regard to the causes of this variation Caccuri (62) reported a diminution in numbers after severe exercise. Degkwitz (72) found that the numbers increased when the temperature was raised. Wittkower [13] noted that after a hot bath the platelets increased from 220,000 to nearly 300,000.

Considering the delicacy of the platelet's structure, the ease with which it can be made to disappear from the blood-stream and the rapidity of its re-

[11] Cited from Osler and McCrae (169). [12] Cited from Reimann (187).
[13] Cited by Leschke and Wittkower (149).

appearance in certain conditions, the readiness with which it disintegrates outside the body, and the way it adheres to injured vascular endothelium, or to foreign bodies introduced into the circulation, it is likely that the life of the platelet is short. Duke (77, 80) found that the total number of circulating platelets could be regenerated within three to five days. Apart from experimental work, and on clinical evidence alone, it is probable that platelets are produced and destroyed in very large numbers each day. It is not surprising, therefore, that the number of these elements in the blood should vary so greatly at short intervals even in health.

Numerical Variations of Platelets in Disease.

The numerical variations may range within much wider limits than in health. From a survey of the platelet counts in the series of cases investigated certain interesting facts emerge. Thus the number of circulating platelets may vary with the disease and also in the same illness according to the stage, whether acute or convalescent. Furthermore, the behaviour of the platelets seems to depend on the reactive power of the individual bone-marrow, which in turn can be influenced by X-rays, phenylhydrazine hydrochloride, liver, and splenectomy. More detailed reference to these changes will be made below.

The great variability in the platelet numbers makes it difficult and of very doubtful value to classify the diseases according to the platelet count. It can be stated, however, in a very general way that the platelets were diminished in acute myeloblastic leukaemia, splenic anaemia, *malignant endocarditis*, pernicious anaemia (relapse), *acute tonsillitis*, lobar pneumonia (precritical stage), and *pyaemia*. They were normal or only slightly diminished in Henoch-Schönlein purpura and static purpura, in scurvy, haemophilia, acholuric jaundice, *diabetes mellitus*, *pelvic sepsis*, and *hyperthyroidism*, while in chronic myeloid leukaemia, pernicious anaemia (remission), secondary (post haemorrhagic) anaemias, lobar pneumonia (convalescence), *acute rheumatism*, *nephritis*, malignant disease, and chronic forms of tuberculosis the platelets were normal or increased in number. In purpura haemorrhagica and polycythaemia vera they were found in some cases to be diminished and in others to be increased. With regard to the diseases underlined it has not been possible to find any publications dealing with the platelet count in these conditions. Apart from these the observations made agree in a general way with those reported by other authors. The only unusual feature recorded is the high platelet count observed in cases of purpura haemorrhagica.

Platelet Morphology in Disease.

During the investigation into the numerical variations of platelets in disease it was noticed in many cases that the size, granulation, and staining reaction varied somewhat from that of the normal platelet. Very small or very

large (giant) forms were observed, and the number of granules in the platelets was frequently found to be increased or diminished, and, further, it was noticed that the cytoplasm in some cases was definitely basophil when stained with brilliant cresyl blue.

For the purpose of investigating the significance of variation in size, granulation, and staining reaction of the platelet in disease it was necessary to have some normal morphological standard. I found great difficulty in grouping the platelets according to the number of granules contained in the cytoplasm. Frequently the granules were congregated together to form a pyknotic mass, but even where they were scattered it was impossible in many instances to count them. They were placed in the following rather arbitrary groups: (*a*) Those in which no granules were apparent; (*b*) those in which there was a marked diminution in the number of granules; (*c*) those in which, in spite of some variation in the number of granules, experience showed that the granulation present could be regarded as being within normal limits; and (*d*) those in which there was a very definite increase in the granular content. This classification is not wholly satisfactory, but although it lacks mathematical precision it is useful, when used by the same individual, as a means by which daily observations on the granulation of platelets could be recorded and compared.

From a study of the morphology of the platelet in disease it was found that the platelet picture was constantly changing, even within the short period of one or two days. It is very difficult, therefore, to draw any definite conclusions as to the significance of this constant change. However, when a large series of observations is made and the platelet picture considered, together with the platelet count and the state of the patient, it is possible to show that the changes observed conform to certain broad general rules and give some idea as to the influence exerted by the disease process on the platelet-producing tissues.

The changes in the platelet picture in certain diseased conditions may be briefly set forth as follows:

Purpura haemorrhagica. (3 cases.) Some little attention has been paid to the morphology of the platelet in this disease, and it seems to be agreed that varying numbers of large platelets appear in the blood.[14] With regard to other changes Fegler (87, 88) found that over 90 per cent. of the platelets were very granular, and Rockwood and Sheard (189) described the platelets in purpura haemorrhagica as varying in size, shape, and type of granulation from those found in a case of pernicious anaemia, the platelet granules in the former disease being very coarse. Glanzmann (100) described the presence of very large and very small forms, basophilia in varying degree, pyknosis of, and variation in the number of, granules, absence or diminution, rather than increase, being the rule. Certain writers have attributed to these apparently abnormal platelets some part in the pathogenesis of purpura haemorrhagica.

[14] References 46, 124, and 159.

Examination of the platelet picture on several occasions in three cases of purpura haemorrhagica did not reveal any marked departure from the normal, but at the time of examination the platelet count in these cases was not diminished. On certain dates two of the cases showed irregular distribution of the granules, some platelets showing diminution, and others increase, in granulation. The granules, however, did not differ in size or shape from those seen in health. The size and staining reaction of the platelets were always normal.

Acute myeloblastic leukaemia. (1 case.) Variation in size of the platelets was observed, increase in the number of small forms being a prominent feature from time to time. In the earlier observations many platelets were packed with granules, but as the platelet numbers diminished the granules became fewer in number.

In *chronic myeloid leukaemia* (1 case) large platelets were present and on the whole there was a decided increase in granulation. Basophilia was rare.

In *splenic anaemia* (1 case) diminution in the number of granules contained in the platelets was the outstanding feature.

Acholuric (haemolytic) jaundice. Splenectomy. (1 case.) Before operation deficiency in granulation was noted. After splenectomy many large platelets appeared in association with a rapid increase in the platelet count. At this time also the platelets became less granular, and many of those present showed a basophil cytoplasm. After the numbers had reached their highest values the platelet picture became normal in every respect.

Malignant endocarditis. (2 cases.) Throughout the period of observation in these cases the platelet numbers were diminished. Very small, normal, and large platelets were present, and there was an increase in the number of basophil forms. The granules were irregularly distributed, and though a few platelets were very granular a greater proportion showed deficient granulation.

Pernicious anaemia. (3 cases.) When the platelet counts were low there was marked variation in size with however a preponderance of small platelets. Many were deficient in granules and basophilia was not uncommon. As the patients improved in health the size became uniform, the amount of granulation increased, and basophilia was not so frequent.

Anaemia secondary to haemorrhage. (9 cases.) In secondary anaemia Fegler (87) has observed that the granular platelets tended to be diminished in number. Larrier (168) and Degkwitz (72) found that the number of large forms of platelet was increased.

In the cases examined there was marked variation in size with a tendency to increase in the number of large platelets. Basophilia was common during the period of rise in the platelet count. The granules were often irregularly distributed, but usually there was an increase in those forms showing defective granulation, which was generally a feature during the period of platelet increase.

Lobar pneumonia. (3 cases.) In this disease Reimann (187) found that

in the precritical stage the average platelet was distinctly smaller and the protoplasm more granular than in the later stages.

In my cases diminution in the number of granules was noted in the early days of the illness. Later the granules became uniformly distributed, although, in one case, unequal granulation persisted throughout the whole period of observation. During the precritical stage in two cases very large and very small forms were present. Basophilia was present before the crisis in one case.

Acute rheumatism (*rheumatic fever*). (7 cases.) Increase in the number of platelets sparsely filled with granules was the rule during the acute stage of the illness, although it was a prominent feature even in convalescence. On the whole the size was normal. Basophilia was uncommon.

Chronic tuberculosis. (2 cases.) In tuberculous peritonitis Stahl (204) found isolated small basophil platelets. In my cases frequent basophilia was the only deviation observed from the normal picture.

In the following diseases a study of the morphology of the platelet did not reveal any typical or noteworthy changes: *diabetes mellitus* (6 cases); *malignant disease* (6 cases), *pelvic sepsis* (1 case), *pyaemia* (1 case), and *hyperthyroidism* (1 case).

The information obtained from the study of the foregoing cases may be summarized thus. When the platelets are diminished in number variation in size is common, the size varying from less than 1 micron to as much as 5 microns. On the whole there is an increase in the number of small forms. During a period of platelet increase the forms tend to be larger in size.

Diminution in the number of granules contained in the platelets is typically seen during the acute phase of an illness when associated with reduction in the number of platelets. Diminution may also be observed when the numbers are increasing or are already high. In convalescence the platelets become more granular.

Basophilia is a notable feature when the platelet count is diminished and also when the platelets are increasing in number.

It would thus appear that variation in size and unequal or diminished granulation appear in conditions in which there is diminution in the platelet numbers and also in states where there is hurried production. If, in addition, there is basophilia (basophilia being a sign of immaturity), it may be assumed, from the presence of these immature platelet forms in the circulation, that the platelet-forming tissues are not producing mature platelets as fast as they are being required. As would be expected these youthful forms are found in all thrombocytopenic states and in the period of increase in the platelet numbers which may follow haemorrhage or splenectomy, or thrombocytopenia from any cause.

With regard to the morphology of the platelet in purpura haemorrhagica it will be apparent, from a consideration of all the points, that all the platelet types described by others as being peculiar to that disease, with the possible exception of the type having coarse granulas, have been observed in other

diseases, particularly when the number of platelets was diminished. It is likely that the presence of abnormal platelets is a feature of thrombocytopenia, no matter how it is produced, and is not peculiar to, or characteristic of, the thrombocytopenia of purpura haemorrhagica.

As a corollary to this conclusion it follows that in purpura haemorrhagica the morphological abnormalities observed in the platelet by others do not afford good evidence that this element is functionally inefficient. The most that can be said for them is that these deviations from the normal indicate immaturity. Similar abnormal forms are present in the blood in diseases which are not characterized by purpuric haemorrhages, and, conversely, these forms may be absent from the blood in conditions in which this haemorrhagic tendency is present. The haemorrhages characteristic of the disease are therefore not due to inherent defects in the platelets.

Cause of Variation in the Platelet Count in Disease.

The problem why there should be such great variation in the platelet count in disease is difficult to explain in view of the uncertainty which exists regarding not only the origin, function, and destruction of these elements, but also the pathogenesis of some of the diseases investigated. The idea that the platelet is produced in the bone-marrow, probably by the megakaryocyte, is reasonable, and when considered along with what is actually known of the pathogenesis of the diseases examined some conclusions may be drawn as to the reason for these variations.

Thus in *acute myeloblastic leukaemia* the reduction in the number of platelets would be explained by the fact that the hyperplasia of, and great activity in, the white cell-producing tissues of the bone-marrow would crowd out the platelet-forming cells. In my case a rapid increase in the number of immature white cells coincided with steady diminution in the platelet count.

With regard to *chronic myeloid leukaemia*, in which disease the platelet counts were found to be increased or within normal limits, it is probable that the variations in individual patients will depend on the degree of activity in the leucopoietic and platelet-producing tissues in each case. Thus the activity of both may be slightly or greatly increased, or, although both are active, the activity of the white-cell tissues may be relatively much greater than that of the platelet-forming tissues.

This difference in the degree of activity in each of the components of the formative tissues of the bone-marrow was demonstrated by three cases of *polycythaemia vera*. In one the red cell count was very high while the leucocyte and the platelet counts were low, suggesting that erythropoiesis predominated in the bone-marrow. In a second case a moderate erythrocytosis was associated with a slight leucocytosis and a very slight increase in the platelet count, while the third case illustrated the association of polycythaemia with a greater leucocytosis and a platelet count which was somewhat lower than that

of the previous case. The two last cases illustrate a state of generalized activity in the bone-marrow, no one tissue reacting to the exclusion of the others.

In *pernicious anaemia* the number of platelets is diminished. It is likely that the platelet-forming tissues in common with the erythropoietic and leucopoietic tissues are also influenced by the pathological process responsible for this disease. The improvement in the patients brought about by liver treatment is reflected as much by the increase in the number of platelets as by the increase in the number of red cells.

The inference that the activity of the bone-marrow in *splenic anaemia* is inhibited is justified by the presence of anaemia and leucopenia and by the absence of signs of regeneration on the part of the red- and white cell-forming tissues. It is likely that the activity of the platelet-producing cells is also diminished, and in this way reduction in the platelet count results. There was no evidence in the case of splenic anaemia investigated that the spleen was hyperactive in destroying blood elements.

The increase in the number of platelets which occurs in *secondary anaemias* has been recognized for some time, especially in those cases where the anaemia has followed haemorrhage. After rabbits had been bled Bunting (59) and Degkwitz (72) found that the platelets increased in number. Many of the cases included in this group showed an increase in the platelet count. In the few cases in which there was no reactive increase the bleeding was slight.

With the exception of one case the platelet increase or reaction was well marked in all the cases in which much blood had been lost, and it must be assumed that loss of blood was the cause. Even in the one case in which there was no reactive increase the presence of large numbers of immature platelets suggested that the platelet-producing tissues were active. The rise and fall in the platelet count was observed to take place during the haemorrhage, or, more frequently, the increase commenced during the bleeding and reached its height after all sign of blood loss had disappeared. Sometimes the increase in numbers was not observed until after the haemorrhage had ceased. In two cases a secondary rise and fall in the platelet numbers was noted a considerable time after the haemorrhage.

Is this platelet reaction the result of an increased functional demand for platelets in view of the part these elements are said to play in haemostasis, or is it merely a regenerative response on the part of the formative tissues to make good the platelets lost in the bleeding? In light of the observation that where the bleeding was slight there may be no platelet increase, and the fact that the peak of the increase frequently occurred when the haemorrhage had ceased and no platelets were required for haemostatic purposes, it seems to me that the platelet reaction is a regenerative process and reflects the state of generalized activity occurring in the haemopoietic tissues of the bone-marrow when a loss of blood has to be made good. This conclusion is all the more justified when one tries to explain the secondary rise and fall in the platelet numbers which was observed in the two cases in the absence of haemorrhage.

In both cases the bone-marrow at that time was in a reactive and unstable condition, as shown by the continued rise in the number of red cells.

Diseases Characterized by Infection and Toxaemia.

All the conditions considered under this heading gave some evidence of the presence of an acute infective process, and for the most part were distinguished by the behaviour of the platelet curves. These showed that in the acute phase of the illness there was a tendency for the platelets to become diminished, and that, during convalescence, the platelet numbers tended to increase, after which there was a gradual fall to within normal limits.

A few observations have been made on variation in the platelet counts in disease. Thus in pneumonia (187), diphtheria (78), scarlet fever (44, 204), and the common cold (25) the platelets have been found to be diminished in number in the acute stage of the illness and increased in convalescence. They have also been reported as reduced in influenza,[15] haemorrhagic smallpox, and typhus (191, 204).

The result of the present investigations is in general agreement with these findings. In *malignant endocarditis* and *pyaemia* the platelets became progressively reduced until death supervened, and in the cases which were complicated with *acute tonsillitis* and *pyuria* a diminution in the platelet counts was observed. In two of the three cases of *pneumonia* the platelets were reduced to below 200,000 at some time during the acute period of the illness, but in the third case they numbered over 1,000,000 on the fifth day of illness, and although the numbers were subsequently reduced for a few days, the diminution was only relative, as the readings were never below the average number found in health. In all three cases, however, a platelet increase occurred in convalescence.

Acute rheumatism proved to be the exception to the general rule. In this disease the platelets were never diminished when the patient was acutely ill; in fact the platelet numbers were high. Six cases showed some evidence of a platelet reaction, but only in three was it pronounced. The time at which this platelet increase occurred differed from that observed in pneumonia in that it took place in some patients during the acute phase of the illness and in others during convalescence.

The almost consistent behaviour of the platelet counts which has been observed in the course of infective illnesses, with the exception of rheumatic fever, suggests that the platelet has an important function, and it is of interest to consider at this stage some of the experimental work and the conclusions derived therefrom which have some bearing on the subject. Certain writers think that the platelet is an active agent in eliminating foreign bodies from the blood or plays some part in establishing a state of immunity to infection. I am unable to agree with either of these views.

[15] References 72, 125, 187, and 204.

Levaditi (150), in 1901, noted that cholera spirilla when injected into the circulation of vaccinated guinea-pigs sometimes became adherent to blood-platelets. Some ten years later Aynaud (21) observed that certain organisms brought about *in vitro* agglutination of platelets. Bull, in a series of publications,[16] reported that streptococci and pneumococci were rapidly removed from the blood of experimental animals unless they were extremely virulent. He further observed that typhoid bacilli and dysentery bacilli of the Flexner group were simultaneously agglutinated in the blood-stream, although in the case of the pneumococcus and the Shiga strain of dysentery bacillus agglutination occurred only when an anti-serum was injected into the circulation. In both cases the agglutinated organisms were rapidly removed from the blood-stream and destroyed in the visceral capillaries. Any bacteria not so agglutinated remained in the blood and produced a septicaemia. None of these observers concluded that organisms were removed from the circulation by the platelets.

Delrez and Govaerts,[17] following up the work of Bull, demonstrated that in the blood-stream of the rabbit staphylococci and paratyphosus B bacilli adhered to the platelets. This adhesion was associated with the disappearance of bacteria from the blood-stream and a diminution in the number of circulating platelets. Two minutes after injection, mixed masses of platelets and organisms were found in the capillaries of the liver and the spleen. This phenomenon was not observed when a virulent pneumococcus was injected into the rabbit. In the dog, however, the same virulent strain of pneumococcus united with the platelets and both disappeared from the circulation. Continuing these investigations Govaerts (109) found that intravenous injection of washed blood-platelets accelerated the elimination of typhoid bacilli from the blood. He observed also that the red cells of the sheep, after exposure to rabbit plasma, were agglutinated *in vitro* by the platelets of the rabbit (106). The same occurred in other animals when foreign red cells or particles of Indian ink were injected into the blood (103, 107).

All this work suggests that the platelet plays a part in maintaining the sterility of the blood-stream. Govaerts [18] considered that adhesion of organisms to platelets was comparable to the first steps in phagocytosis, and he thought that it depended on the opsonic action of the plasma on the foreign matter. In addition Popesco demonstrated (*a*) that platelets from immunized and non-immunized animals prevented haemolysis by staphylolysin (179), (*b*) that well-washed platelets from immunized rabbits when in contact with fresh serum brought about granular change in the cholera spirillum, whereas this alteration was not produced by platelets from non-immunized animals (180), (*c*) that the platelets of the rabbit immunized against red cells of an animal of another species produced haemolysis when brought into contact with these red cells (181), and (*d*) that platelets from a rabbit immunized against the cholera spirillum when injected into guinea-pigs afforded some degree of immunity to

[16] References 53 and 56 inclusive. [17] References 73, 107, and 111.
[18] References 104, 105, 107, and 110.

these animals (182). This same writer working with Combiesco (183) also demonstrated that the watery extract of platelets of a suitably immunized rabbit had a protective action against the cholera spirillum. A similar extract from non-immunized animals was not nearly so effective in its action. From these findings it would seem that the platelet takes some part in keeping the body immune from infection.

The work of Govaerts and Popesco thus suggests an explanation for the reduction in platelet numbers observed in acute infections. Diminution in the count would be due to the using up of platelets in removing and destroying the infecting agents. It is interesting to note that absolute or relative diminution in the platelet count occurred in many of my cases in which bacteraemia was present or probable. Further it was noted, when intravenous injection of T.A.B. vaccine was given to a patient suffering from rheumatoid arthritis, that the platelets in the capillary blood steadily diminished in number for twenty-five minutes after the injection. Within two hours they had regained their original level. All these observations are in keeping with the idea that the platelet is an important means whereby the organism is rendered immune from bacterial infection. Accordingly, it would seem reasonable to expect that where the platelet numbers were diminished there would be lowered resistance to infection. Cramer, Drew and Mottram (67, 68) considered that the increased susceptibility to infection found in rats which had been fed on a diet deficient in vitamin A, or exposed to the action of X-rays or radium, was due to the platelet diminution which resulted.

In spite of all the foregoing evidence the interpretation of the reduction in numbers as being due to a using up of platelets in the elimination and destruction of bacteria is not free from objection. Although there may be no doubt that platelets can adhere to organisms and other foreign bodies, it is still not clear that this adhesion occurs to such an extent that the platelets are reduced in number, and it certainly does not follow that this adhesion proves that these elements are really an important barrier against bacterial invasion. It has been mentioned that diminution in the number of platelets did not occur in rheumatic fever, and in one case of lobar pneumonia, although there was a relative diminution, the numbers were never much below 400,000. It is recognized, however, that in acute rheumatism the presence of an infecting organism in the blood is not established beyond doubt, and in the case of lobar pneumonia it is possible that the infecting agent was of a type that did not bring about adhesion of platelets to itself. Even so, these findings tend to cast some doubt on the idea that the platelet is an active agent in maintaining the sterility of the blood-stream, and that the presence of organisms in the blood brings about a reduction in the number of platelets.

Observations made by others may be used to justify this doubt. It has been shown that in diphtheria (78), in which disease the causal organisms are not found in the blood, reduction occurs. The same result can be procured experimentally with diphtheria toxin (79) and the purpuric principle extracted

from the pneumococcus (123, 188). Further, it is not commonly the case that the thrombocytopenia of purpura haemorrhagica and pernicious anaemia is associated with increased susceptibility to infection. Furthermore, it may be said that Bedson and Zilva (37, 38), and Stammers (205) independently, were unable to produce diminution in the platelet count after feeding rats on a diet deficient in vitamin A. Some other explanation will therefore have to be found for the susceptibility to infection which occurs in the absence of vitamin A from the diet.

Bacteria can be eliminated from the blood in the absence of platelets. Govaerts (108) himself noted this on injecting bacillus typhosus into deplateletized animals. Delrez and he (73) also noted that in inoculated rabbits pneumococci were agglutinated and removed from the circulation without any participation of the platelets. Similar observations were also made by Bull and McKee (57), who showed that in immunized and non-immunized animals, whether deplateletized or not, agglutination of bacteria depended on the amount of agglutinin and not on the presence of platelets. They also showed that the presence of these elements in the agglomerations was merely an accidental phenomenon. Furthermore it was shown by Manwaring and Coe (155) that the capillary endothelium of the liver of actively immunized animals fixed pneumococci when perfused with Ringer's solution containing these organisms. This did not occur in the non-immunized liver except when immune serum was added to the perfusing fluid. It is apparent that other factors are concerned in keeping the blood sterile and free from foreign bodies, and it is likely that the sterility of the blood depends on the opsonizing action of the blood-plasma which brings about agglutination of organisms and their adhesion not only to platelets but also to the phagocytes of the blood and to the cells of the reticulo-endothelial system.

The primary importance of the plasma in the elimination of foreign bodies is further emphasized by Roskam (195), who showed that adhesion of opsonized foreign bodies to the platelets was not due to a platelet secretion. He also found that a pellicle of plasma adhered by adsorption to the surface of the platelets so that the adhesion of opsonized organisms and foreign bodies was due to this layer of plasma. Agglutination and adhesion are thus passive phenomena and not the result of any vital activity on the part of the platelet. It should be mentioned, however, that Popesco (181) in his experiments on the haemolytic action of immunized platelets could not attribute the haemolysis to traces of haemolysin which adhered to the platelets. He found that the fluid in which the platelets were last washed did not have any haemolytic power, and conversely, that normal platelets which had been in contact with haemolytic serum and then washed did not possess any haemolytic action.

In spite of these differing observations it seems to me that the blood-plasma plays by far the greater part and that the platelets take a very unimportant part in the elimination of bacteria from the blood-stream; and therefore that in acute infections alteration in the platelet count is due to the presence in the

body of a toxic agent. That the platelet count depends to some extent on the degree of toxaemia is shown by the observation that although larger doses of tuberculin and diphtheria toxin poison, smaller doses irritate, the platelet-producing tissues (79).

It follows that the increase in platelet numbers which has been noted in acute illnesses must be due to one of two causes. When it is preceded by reduction in the platelet count and occurs just before or during convalescence it will be a reactive process due to subsidence of the infection and the removal of toxic inhibition of the platelet-forming tissues. On the other hand, if it takes place when the patient is acutely ill, as in rheumatic fever, it will be due to stimulation of the formative tissues. It is unlikely that increase in platelet numbers has anything to do with the establishment of a state of immunity, for it was observed to occur in a patient in whom there was no evidence of bacterial infection or toxaemia. In this case the rise in the platelet count occurred with improvement in the general health and the onset of a feeling of well-being. It has been shown also that a similar rise in the platelet count occurs in the convalescence which follows surgical operations[19] and parturition (71) in the absence of sepsis.

According to my view the platelet increase, which so often occurs in convalescence, merely reflects the state of bone-marrow activity and as such may be brought into line with the increase noted in the haemorrhagic group.

The Platelet Count and Purpura Haemorrhagica.

The blood-platelet has been described as 'the guide in the labyrinth of purpuric diseases', and it is now the custom to regard the great diminution in the platelet count in purpura haemorrhagica as the essential lesion and the one which separates it from the other purpuric diseases. There are two main theories each of which attempts to explain this reduction in the platelet numbers.

The one attributes the diminished count to toxic injury of the megakaryocytes in the bone-marrow. The myelotoxin is thought to arise in the spleen, and the good results which follow splenectomy are said to be due to the removal of the source of the toxin.

Greater support has been given to the other theory in which the spleen is regarded as being overactive in destroying platelets (124). In support of this idea it has been shown that the blood-platelets in purpura haemorrhagica are frequently very large and that there is an increase in the number of megakaryocytes in the bone-marrow, thus suggesting regenerative activity rather than inhibition. Adherents of this theory think that the presence of many platelets within the spleen, when contrasted with the thrombocytopenia of the blood, is evidence of increased destruction of these elements. Also the fact that there

[19] References 32, 36, 71, 120, and 149.

is an immediate rise in platelet numbers after splenectomy is to them additional proof that the spleen is hyperactive in platelet destruction as it is unlikely, if the bone-marrow were injured, that the platelet increase would be so sudden. They explain the cases in which there is a gradual return of the platelet numbers, after splenectomy, to their former low level, and those cases in which removal of the spleen is not followed by an increase by stating that other parts of the reticulo-endothelial system have taken over the function of the spleen, or that the whole of this system has been hyperactive from the beginning. It is known that vicarious hyperplasia of the reticulo-endothelial system may occur in splenectomized animals (171).

In spleens removed from patients suffering from purpura haemorrhagica the most constant of the changes reported has been primary or secondary proliferation of the reticular cells in the sinuses and Malpighian bodies.[20] Some observers noted the presence of platelets or platelet-like substances within the endothelial cells, but others could not find, and some did not look for, any evidence of platelet destruction. Sutherland and Williamson (207) found endothelial proliferation in a lymph gland.

The presence of more platelets in the spleen than are present in the blood is not sound proof of increased destruction because the spleen acts as a reservoir for platelets. Again, endothelial proliferation in the spleen might indicate that this organ was the source of some altered secretion which upsets platelet production. Further, direct evidence of platelet destruction is not very convincing. In addition, a very quick increase in the platelet numbers comparable to that occurring after splenectomy may occur where there has been toxic inhibition of the bone-marrow: rapid spontaneous increases were noted in many toxic cases investigated by me.

Seeliger (201) found in half of his cases that the number of platelets in the spleen was increased, and he was of the opinion that in these cases this finding was evidence of destruction of defective platelets. In the remaining cases he got no evidence either of increase in the number of platelets in the spleen or of increased destruction of these elements. In two cases there was no diminution in the number of megakaryocytes, but these giant cells showed signs of nuclear degeneration and were deficient in granules; indeed many were agranular. Seeliger thought that the platelet diminution in purpura haemorrhagica was due to toxic disturbance interfering with the normal functioning of the megakaryocytes.

At this stage it is necessary to take a wider view of the subject. In four cases of purpura haemorrhagica investigated by me marked thrombocytopenia was observed only in one. In another case the platelets were never lower than 140,000. The two remaining cases always showed high counts. Morphological examination of the platelets in the last three cases did not give any clue, as would be suggested by the presence of immature forms, that the higher counts were due to increased platelet production in order to counteract excessive

[20] References 48, 65, 99, 124, 128, 166, 167, 201, 203, and 207.

platelet destruction. From the evidence afforded by these cases it is apparent that in purpura haemorrhagica the platelets may vary numerically within wide limits.

Thrombocytopenia may be present, or the platelets may be moderately diminished, normal, or slightly increased in number, in the presence of purpuric symptoms. Further, spontaneous increase in the count occurred in one case. Others have recently reported cases in which there was no reduction in the number of platelets,[21] and Forster's cases (94) illustrate that spontaneous numerical increase may occur without surgical interference.

It is very doubtful, therefore, if thrombocytopenia is the cause of the characteristic lesions and of any real importance in the differentiation of purpura haemorrhagica from the other purpuric diseases. Rather it would seem that the platelet count varies independently of the haemorrhages and that the platelet diminution, although very commonly associated with this disease, is merely a superimposed phenomenon. Tidy (214) is of the opinion that fall in the platelet numbers is secondary to damage of the capillary endothelium and loss by haemorrhage. This hypothesis is not supported by the knowledge that in other diseases in which there is damage to, or alteration in the permeability of, the capillaries, as in scurvy and Henoch-Schönlein (anaphylactoid) purpura, the platelets are not greatly diminished. With regard to the latter disease it has been found that in experimental anaphylaxis the transitory diminution in the number of platelets is due to agglutination of these elements and not to demands made on them for protection of capillary walls.[22] In two of my four cases of purpura haemorrhagica the presence of platelets in increased numbers did not prevent capillary haemorrhage. This would be unlikely if the platelets protected the capillary walls. Again, there is no apparent reason why diminution in the platelet numbers should be present in this disease if the platelets are merely used up in protecting the capillary vessels, seeing that the bone-marrow is active, or potentially active, as shown by the presence of megakaryocytes in normal or increased numbers and the frequent increase in platelet numbers which immediately follows splenectomy. Loss of platelets by haemorrhage would not account for the diminution as the platelets may be greatly reduced in some cases and yet the bleeding may be very slight. It is evident that some other factor is necessary to explain the thrombocytopenia, which is frequently, but not always, present.

I think that the diminution in the platelet count so often found in purpura haemorrhagica is a secondary or coincident phenomenon and not the essential cause of the illness. I have found that in diseases in which there is undoubted toxaemia a reduction in the number of platelets is a frequent occurrence, and that a spontaneous increase follows when the toxic disturbance passes off. In all probability the variations in the platelet count found in purpura haemorrhagica are somewhat similar to those observed in toxaemic diseases. The 'toxic' disturbance may not be of the same type as met with in acute infections, and,

[21] References 100, 152, and 196.

[22] References 10, 11, and 12.

considering the variations in the number of platelets, it may vary in intensity, Indeed, the interference with normal platelet production may be due to some metabolic disturbance or to deficiency of some internal secretion. It is not altogether a new thing to have marked diminution in the platelet count produced by lack of some essential substance, for, in pernicious anaemia, an increase occurs in the platelet count immediately liver is added to the diet. According to this hypothesis the diminution in platelet numbers found in purpura haemorrhagica is due not to excessive destruction of platelets but to interference with normal platelet formation.

Other Factors which modify the Platelet Count.

Influence of X-rays on the platelet count. Frank (97) has reported cases of leukaemia in which, after treatment with X-rays, the platelets became reduced in number. Diminution in platelet numbers has also been produced by Roentgen rays in animals (130, 164).

The effect of radiation on three cases of leukaemia and two of polycythaemia vera varied. In one case of acute leukaemia the platelet decrease which ultimately resulted seemed to be due to increase in the white cells rather than to the X-ray treatment as the platelets were diminishing, and the leucocytes increasing, in number before X-ray treatment commenced. In two cases of chronic myeloid leukaemia the platelets were diminished after irradiation in one case but not in the other. In one case of polycythaemia vera, the platelet count was not influenced in any way, and in the other, although the numbers ultimately fell to below 100,000, the impression was gained that at the beginning of treatment the Roentgen rays stimulated the platelet-forming tissues. In all the cases an erythema dose of deep X-ray therapy was given at each exposure, but the total number of doses given varied in each case with the response to treatment.

From the results of my observations no very satisfactory conclusions emerge, but it is apparent that, although the platelet numbers may be diminished by X-rays, the effect varies with the patient and possibly with the disease.

Influence of phenylhydrazine hydrochloride on the platelet count. This drug was used in the treatment of two cases of polycythaemia vera (153). In each case the red cells became reduced in number, but the presence of reticulocytes and polychromasia showed that an active process of red cell regeneration was going on side by side with destruction. This, together with the leucocytosis and increase in the number of platelets, pointed to activity of the bone-marrow. The increase observed in the platelet count is probably similar to that which is present after severe haemorrhage, and is merely an expression of generalized haemopoietic activity.

Influence of liver on the platelet count. Whipple, Hooper, and Robscheit (221) found that liver was very efficient in promoting complete blood regeneration. Minot and Murphy (163) were the first to treat pernicious anaemia with that

substance. The five cases of pernicious anaemia investigated by me showed diminution in the number of platelets, and it was of interest to observe that under liver treatment the platelets increased in all the cases, although in one the count was never very high. In the remaining four cases the counts increased to within normal limits. In three of these cases the numbers reached beyond 400,000, but in the fourth the platelet increase was unusual in that it showed a very rapid rise to the high value of over 900,000 and then a gradual return to the 400,000 level. The platelet-forming tissues participate in the general improvement in haemopoietic activity produced by liver.

Influence of splenectomy on the platelet count. In one case of acholuric jaundice, after splenectomy, the platelet numbers were maintained at a high level, the count, three and a half months after operation, being nearly 700,000. This finding supports the view that the spleen removes and destroys platelets. It must be remembered, however, that after other operative procedures an increase in the platelet count occurs.[23] This increased platelet count due to surgical operation does not become evident until about the sixth day after operation, and normal numbers are reached within about three weeks. It may be concluded, therefore, that the behaviour of the platelets after splenectomy is due to the removal of the spleen and not simply to the surgical measures involved.

Blood-platelets and Coagulation.

A number of observers attribute to the platelet an important function in coagulation. Others think that alteration in the blood-plasma alone is responsible for the inception of the clotting process.

Hayem (113) and Bizzozero (43) found that fibrin was formed only where platelets had accumulated. In coagulation the platelets of frog's blood undergo agglutination and rapid disintegration (184), and they are found where strands of fibrin cross each other (209). Moreover, in certain crustaceae, the 'explosive corpuscles' first disrupt and then become the centres of coagulation (208). A similar platelet cytolysis is said to inaugurate spontaneous coagulation in human blood, the fibrin being most dense where cytolysis is most abundant (210–12). Wright and Minot (224) thought that agglutination and fusion of platelets in shed blood was intimately associated with the early stages of coagulation. Tait and Burke (210) considered that thrombin was liberated on lysis of the platelet. Howell (118) and others (29, 121) believed the platelet to contain prothrombin and thromboplastin. Morawitz (165) thought it contained thrombogen and thrombokinase, while Bordet (45) regarded the platelet as one of the sources of cytozyme.

Coagulation occurs only in the presence of free calcium, and it has been thought that calcium causes lysis of the platelet and thus inaugurates clotting. Many of the substances which preserve the platelet fix calcium and inhibit

[23] References 32, 36, 71, 120, and 149.

coagulation. On the other hand, platelet extracts reinforce and accelerate clotting.[24]

Deplateletized mammalian blood clots but slowly (118, 210), and Burke and Tait (61) considered that wholly deplateletized blood would not clot spontaneously. Filtered oxalated plasma is deplateletized, and clotting fails to occur on the addition of calcium chloride (69). Coagulation of lymph and hydrocele fluid can be initiated and hastened by platelet extracts, the greater the number of platelets or the greater the quantity of extract added the more rapid is coagulation and the richer the coagulum in fibrin (45). It would seem, therefore, that the platelet is essential not only for the initiation of coagulation but also for the acceleration of the process.

A number of observers, however, deny to the platelet such an important function. They consider that coagulation depends on the plasma and not on the platelet. Denys (74) found that fibrin could be laid down without platelets. Achard and Aynaud observed that agglutination of platelets occurred independently of coagulation (1) and that these elements could remain isolated and independent of the fibrin network (9). Moreover, platelets can be preserved on oiled or paraffined surfaces when the first stage of clotting has occurred.[25] In deplateletized blood it has been found that the blood coagulated and retracted rapidly (7). Conversely, incoagulable peptone blood does not coagulate in the presence of platelets (5, 176). With regard to filtered blood it has been pointed out that the filter holds back various plasma proteins so that earlier portions of the filtrate do not clot while later portions coagulate readily (101). These observations suggest that it is the plasma and not the platelet which is the important factor in coagulation.

It will be seen that the position of the platelet in the process of coagulation is not definitely settled. It would seem that the inception of clotting is due rather to primary alteration in the stability of the colloidal equilibrium of the plasma. Pickering and Reeves (177) found that the platelet-free plasma of birds contained all the essentials necessary for coagulation. Apparently, however, platelets and their extracts can accelerate coagulation. In this connexion it is difficult to exclude the possibility that the acceleration is due to the presence in the extracts of traces of the plasma from which the platelets were derived. It has been shown that such plasma is adsorbed to the platelet surface (89, 195). Even so it is probable that platelets and their extracts hasten coagulation. Under this assumption platelets are not responsible for the commencement of coagulation. They would, however, exercise an important influence on haemostasis in that they would accelerate clotting.

The relationship between the duration of clotting time and the number of platelets in the circulation at the time of bleeding is still unsettled. Roskam (191) found that the clotting time remained more or less constant, although the platelet count varied from over 400,000 to about 33,500. In certain diseases showing thrombocytopenia Rosenthal (190) did not find any change in the

[24] References 45, 69, and 126.

[25] Burker, cited from Pickering (172).

clotting time. Other authors [26] have not found any relationship between the number of platelets in the circulation and the coagulation time. On the other hand, Evans (85) and others (71, 198) were inclined to favour the idea that duration of clotting time varied inversely with the number of platelets in the blood. In influenza increase in the clotting time has been attributed to reduction in the number of platelets (125). In the acute phase of lobar pneumonia some authors found the coagulation time to be shortened (15) and others found it to be prolonged (75, 162). In none of my cases of lobar pneumonia did the coagulation time vary in any constant fashion with alteration in the number of circulating platelets.

These observations serve to illustrate the diversity of opinion on the relationship between the number of circulating platelets and the duration of coagulation time. As the result of my inquiry I found that in practically every case the two varied independently of each other. For example, in one case the coagulation time was 1 min. 45 sec. when the platelets numbered 1,970 and 2 min. when the number was 194,035, or, as shown by another case, when the clotting time was constant at 1 min. 45 sec. the platelet count on separate days was 377,585 and 1,007,770.

In haemophilia delay in coagulation has been ascribed to qualitative change in the haemophilic blood-platelet. Addis (13) showed that there was delay in the formation of thrombin from prothrombin. Minot and Lee (161) thought that the haemophilic platelet failed to give up prothrombin readily. They demonstrated that normal platelets shortened the coagulation time of haemophilic blood, although haemophilic platelets when added to haemophilic blood shortened the coagulation time only very slightly. Doubt has been thrown on the value of their work by Roskam (195) and Feissly (89), both of whom have shown that washed platelets are active only because of the plasma which is adsorbed to their surface. Thus it appears that the defect in the coagulability of the blood in haemophilia is present in the plasma itself and not in the platelets. This is also the view of Pickering and Gladstone (173, 174).

From a consideration of the experimental work it is probable that the platelet accelerates coagulation. However, from the evidence afforded by the clinical data obtained by me, it is apparent that the number of platelets in the circulation is no guide to the rapidity with which clotting occurs when blood is shed. On this account it is very doubtful if the platelet factor in the clotting process is of more than secondary importance. Coagulation of extravasated blood is a very complex phenomenon, and the results of my clinical observations seem to strengthen the idea that coagulation depends primarily on the state of colloidal equilibrium of the plasma.

Blood-platelets and Thrombosis.

The white thrombus is composed of blood-platelets. Bizzozero (43) watched the gradual accumulation of platelets when the vessel wall was damaged,

[26] References 70, 74, 113, and 202.

and Eberth and Shimmelbusch (84) showed that when the blood-flow was slowed down the platelets passed into the periphery of the stream before adhering to the injured surface. When the lumen of the vessel becomes closed in the neighbourhood of the white thrombus the column of blood becomes stationary and rapidly forms the red thrombus.

Since the white thrombus is made up of platelets it is of considerable importance to understand what relationship the number of platelets circulating in the blood bears to the occurrence of thrombosis. Rosenthal (190) pointed out the coincidence between thrombosis and an increased platelet count in certain cases, and Dawburn, Earlam, and Evans (71) showed that the clinical tendency to thrombosis and pulmonary embolism commonly occurred during a period of platelet increase. In thrombocytopenic purpura Leschke and Wittkower (149) noted that in three of their patients a rise in the number of platelets preceded thrombosis.

Although the platelet plays a very important role in thrombosis, increase in the platelet count alone is not sufficient to bring it about. In many of my cases a rise in the platelet count to numbers varying between 800,000 and 1,700,000 was noted yet thrombosis did not result. The diseases in which this rise occurred included leukaemia, gastric, and duodenal ulcer with and without haemorrhage, lobar pneumonia, acute rheumatism, nephritis, and malignant disease, in none of which is thrombosis a common feature. Thrombosis is, however, a frequent complication of polycythaemia vera and it occasionally occurs after the operation of splenectomy. It was not observed in either of the two cases of splenectomy investigated. In polycythaemia vera, although a platelet increase occurred in two cases, it was only in one that thrombosis occurred.

It can only be concluded, therefore, that increase in the number of circulating platelets is not sufficient to induce thrombosis, but it is only one of several variable factors; for example, slowing of the blood-stream, damage to the endothelial lining of the vessel wall, alteration in the coagulability of the blood-plasma, and possibly changes in the agglutinability of the blood-platelets.

Blood-platelets and Clot Retraction or Syneresis.

Many authors have shown that retraction depends on the presence of platelets in the blood, and it has been stated that the amount of retraction and extrusion of serum is directly proportional to the numbers of platelets present.[27] This view is not, however, universally accepted.

Hayem (115) and many others have observed that in purpura haemorrhagica clot reaction is absent and asyneresis has come to be regarded as an important diagnostic sign of this disease. Absence of retraction has also been noted in pernicious anaemia, aplastic anaemia, and Banti's disease (190). In

[27] References 18, 78, and 115.

these diseases it is frequently found that when the number of circulating platelets falls below 100,000 the clot formed is soft and jelly-like and there is scarcely any retraction or extrusion of serum. After splenectomy in certain of these diseases retraction of the clot becomes progressively increased coincident with rise in the platelet count.[28]

It has been shown experimentally that retraction occurs only in proportion to the number of platelets present in the blood-plasma (115, 136) or hydrocele fluid (147). *In vivo* experiments have also shown an intimate relationship existing between the platelet and retraction (137, 139). It has been demonstrated that blood from deplateletized animals fails to contract when coagulation is induced until platelets reappear in the circulation.[29] Agents which modify or destroy platelets can influence syneresis. Thus it can be suppressed or retarded by crushing or drying the platelets (147), by heating them to 50–58° centigrade (136), by cooling them to 4° centigrade (16), or by exposing them to the action of anti-platelet serum (137, 139), sulphuric acid, chloroform, ether, saponin, and bile, to distilled water and sodium fluoride (16), and to quinine and chlorcalcium (149). Ageing of the platelets also modifies clot retraction (16, 140). These observations suggest that retraction of the clot is a function of the platelet and that it depends to some extent on the life of this element. Le Sourd and Pagniez (142) were so convinced that syneresis depended on the platelet that they used the presence or absence of syneresis as a guide to the presence or absence of platelets within an organ. Thus they thought that the retractive property of the bone-marrow was due to the presence of megakaryocytes, and therefore these writers favoured Wright's view of the megakaryocytic origin of the blood-platelet (143, 144).

Frank (95) thought that in the process of coagulation shrinkage of the little group of platelets set in the knots of the fibrin network brought about retraction. Le Sourd and Pagniez (136) were of the opinion that syneresis was due to a platelet 'ferment'. Glanzmann (100) favoured this idea, and he called the ferment 'retractozyme'. Roskam (192), however, failed to find any proteolytic or lypolytic ferments in the platelets of the rabbit or dog.

In spite of the many ingenious experiments and observations some doubt has arisen as to whether the platelets are responsible for clot retraction. In the course of my investigations I found that syneresis of the clot was not proportional to the number of platelets in the blood. It was noted in many instances that with the same number of platelets the amount of retraction varied, and conversely, that the same degree of syneresis was present when the platelet counts were at widely different levels. These differences were evident not only in the same case but also when different cases were compared. In certain cases syneresis was present but 'poor' in degree when the platelets were below 10,000 and 'fair' at counts between 20,000 and 40,000. At these values, according to prevailing opinion, retraction should be absent. In the literature I have been able to find two references reporting the presence of

[28] References 47, 85, 86, 99, and 124.

[29] References 131, 134, and 135.

retraction when the platelets numbered 28,000 in one case (124) and just below 50,000 in the other (44). Conversely in other cases retraction was absent when the platelets were between 140,000 and 160,000, between 300,000 and 500,000, and also at the high value of 1,000,000. In addition to this the degree of syneresis was 'poor' at counts varying between 200,000 and 500,000. At these figures clot retraction is usually well marked. Even so, other writers have noted that retraction was absent and the serum not extruded from the clot when the platelets were present in numbers varying from 120,000 to over 400,000.[30] Myers (167) observed that in closed tubes of blood, sent for agglutination tests, and Wassermann reaction from cases in which there could not have been essential purpura, there was non-retraction of the clot in 40 per cent. Kaznelson (124), however, on examining many hundreds of samples of blood always found that retraction occurred at room temperatures if blood-platelets were present in high numbers provided the blood was held in U tubes, one millimetre in diameter. When it was contained in ordinary tubes there was sometimes no retraction, even when the platelets were present in large numbers. It is possible that difference in technique may account for some of the contradictory findings, and more especially will this be so in view of the observations of Howell (119) and Pickering and Hewitt (175) regarding the modifications produced in syneresis by adhesion (see below). In this connexion it was noticed that samples of blood from two cases investigated, when contained in an ordinary test-tube, failed to retract and expel serum within twenty-one and twenty-four hours after they had been withdrawn. However, when the blood was gently loosened from the sides of the tubes syneresis occurred very quickly. It must be remembered that adhesion may interfere with syneresis, and in my work care was taken to avoid the fallacy of non-retraction due to adhesion.

From these clinical findings it will be seen that, contrary to common belief, syneresis of the clot may be present when the platelets are greatly diminished in number and that it may be absent even when the platelets number over 1,000,000. It is, therefore, doubtful if the platelet is really the important factor in producing retraction. It may be that its retractile property is modified in disease in such a way that it is hyperactive in these cases in which retraction occurs in spite of low numbers, or diminished in those in which syneresis is absent and the platelet values high. This, however, is improbable as it is unlikely that in the same disease the platelets would be changed or their functions modified to cause retraction in one case and not in another, or that in the same patient syneresis would be absent at higher numbers and present at lower.

The fact that in the precritical stage of lobar pneumonia retraction was absent or diminished when the platelet count was not, or only slightly, diminished must be of some significance. Although it is possible that there is some toxic damage to the platelets it is more likely that the disturbance is

[30] References 63, 100, and 219.

situated in the blood-plasma, especially when one considers that in the acute phase of this disease the fibrinogen content of the plasma is greatly increased (220). Certain experimental findings favour the idea that the blood-plasma is the important factor in retraction.

Achard and Aynaud (7, 11) found that pleural exudate, which contains no blood-platelets, coagulated and retracted, and that these two processes also rapidly occurred when blood was deplateletized by injecting gelatine, electrargol, gum, or lecithin into the circulation. It has also been demonstrated that, during the period of disappearance of the platelets from the blood after intravascular injection of peptone or thymus nucleic acid, the clot retracted (175). Roskam (193, 194) showed that the clot resulting from coagulation in a 'floating drop' of platelet-free plasma contracted spontaneously and gave rise to a considerable quantity of serum, removal of which favoured syneresis. Even from the work of Le Sourd and Pagniez (140) evidence is forthcoming to suggest that other factors might be necessary to bring about retraction of the clot. On adding small quantities of acid they found that irretractile oxalated plasma containing platelets contracted, the acid acting on the plasma rather than on the platelets. When the H-ion concentration of the blood was altered by the addition of calcium other writers found that the irretractile clot of purpura retracted although it was also found that retraction was absent, not only in the absence of calcium, but also in the presence of excess of that substance.[31] All these observations suggest that the plasma is an important factor in the phenomenon of retraction and that it can be so altered that normal syneresis is modified.

More direct proof of the importance of the plasmic factor in syneresis has been furnished by Howell (119). By increasing the alkalinity of blood he discovered that the fibrinogen could be modified to give a structureless gel which was soft and transparent and showed no tendency to retract or express serum. He found also that cell-free oxalated plasma or solutions of pure fibrinogen showed the property of retraction to a marked degree on the addition of thrombin, and he suggested that the blood-platelets were connected indirectly with syneresis in that they might be a source of thrombin. Howell pointed out that adhesion to the walls of the containing vessel inhibited retraction, which, however, appeared when the clot was gently loosened from the sides of the containing vessel. Pickering and Hewitt (175) also discovered that adhesion played a part in the retraction of the plasma gels.

It is therefore very doubtful if the platelet is the all-important factor in bringing about retraction of the blood-clot. I am of the opinion that syneresis depends on the state of the plasma, particularly with regard to the properties of its fibrin content, which can be so altered or modified that different types of gel may be formed in the process of clotting. The platelet hastens coagulation, and as retraction may be regarded as the last act in the completion of clotting it would be reasonable to expect that the platelet extended its influence into

[31] Cited from Leschke and Wittkower.

this phase of the coagulative process. The constancy with which the addition of uninjured and physiologically active platelets to coagulable fluids increases the degree of retraction, and the clinical evidence which demonstrates the association between diminution or increase in syneresis with diminution or increase in the number of platelets respectively, cannot be disregarded. It can only be concluded that the platelet takes some part in bringing about clot retraction. When present in the blood under normal conditions it will bring about an increase in the amount of retraction, but in disease, for example lobar pneumonia, modifications in the plasma will produce changes in the degree of syneresis, which, however, will vary with the extent to which the plasma is altered or modified. Thus in the acute phase of lobar pneumonia the alteration in retractility is not due to the diminution in the number of platelets but to changes occurring in the fibrinogen content of the blood-plasma.

According to my view syneresis of the clot depends on (*a*) the blood-plasma and (*b*) the blood-platelets. Of these the former is the more important, and as it is a very complex and unstable substance it is probable that the varying results obtained on investigation of some of my cases were due to alteration in the retractile property of the plasma rather than to alteration in the retractile function of the platelet. In retraction of the clot the platelet is of secondary importance and serves to augment the retractile property of the plasma.

Blood-platelets and Capillary Haemorrhage.

It has been stated that the tendency to spontaneous capillary haemorrhage exists in proportion to the number of platelets in the circulation. Duke (78) pointed out that where this tendency to spontaneous capillary haemorrhage existed the duration of blood-flow from a freshly punctured wound was prolonged although coagulation time was normal. He showed that prolongation of bleeding time and spontaneous capillary haemorrhage were associated with diminution in the number of circulating platelets. Evidence of this relationship has been found in purpura haemorrhagica, acute leukaemia, pernicious anaemia, aplastic anaemia, diphtheria, haemorrhagic smallpox, and benzol poisoning,[32] and in experimental work with diphtheria toxin, benzol, anti-platelet serum,[33] and X-rays (130, 164). In other purpuric conditions, in which the platelet count was normal or only slightly increased, the bleeding time was found by Duke to be within normal limits. In common with many authors Duke considered that, in order to stop capillary haemorrhage, platelets were necessary because they adhered to the edges of injured endothelium and initiated the formation of a thrombus which closed the wound and prevented haemorrhage.

Certain of my observations throw doubt on the usual explanation that paucity of circulating platelets is responsible for the spontaneous haemorrhages

[32] References 70, 78, 79, 94, 95, 112, and 124. [33] References 126, 131, 132, and 134.

and increased bleeding time met with in purpura haemorrhagica, pernicious anaemia, and acute leukaemia.

In the first place, the number of platelets may be greatly diminished and yet no increase in the bleeding time or no spontaneous haemorrhages result. This was found in one case of splenic anaemia, in which the platelets were diminished to 100,000, and in two cases of malignant endocarditis, in which the platelet numbers were well below this figure. In one case of acute myeloblastic leukaemia, marked diminution in the number of platelets was present for about ten days before any increase in the bleeding time was noted. The presence of a diminished platelet count and the absence of haemorrhage has also been noted by other writers.[34]

Secondly, spontaneous capillary haemorrhage and prolongation of bleeding time may exist in the presence of platelets in the following numbers: 140,000; 750,000; 800,000; and 825,000. These observations were made on four cases of purpura haemorrhagica and one case of jaundice. Somewhat similar findings have also been reported, especially in some cases of jaundice, chronic liver disease,[35] and pregnancy (218). In hepatic diseases and pregnancy, however, the clotting process is frequently delayed, and although increase in coagulation time is not commonly associated with prolongation of bleeding time it is possible that when they occur together delay in coagulation is a factor in altering the duration of bleeding time. In the case of jaundice mentioned coagulation time and bleeding time were both increased together. However, it is noteworthy that in the four cases of purpura haemorrhagica the coagulation time was normal. Roskam (196) and Little and Ayres (152) have recently reported similar cases in which spontaneous haemorrhage and increased bleeding time were both associated with normal platelet counts.

Thirdly, bleeding time may vary within wide limits when the platelets are constantly diminished. Not only so, but in the same person at the same time the duration of bleeding may vary with the site of puncture even when corresponding parts of the body are compared under similar conditions. These points were illustrated by a fair number of my cases.

The above observations—normal bleeding time and absence of haemorrhage in the presence of a diminished platelet count, prolongation of bleeding time and the presence of capillary haemorrhage when the platelets are normal or increased in number, and variation in the bleeding time with change in the site of puncture—are not in keeping with the idea that a diminished platelet count is the cause of prolonged haemorrhage from capillary vessels. They suggest that other factors are concerned in controlling the duration of haemorrhage. Two possible factors exist, namely, alteration in the coagulability of the plasma or alteration in the permeability of the walls of the capillary vessels.

Roskam (195) showed that when a moderate or intense thrombocytopenia was associated with delay in coagulation the duration of bleeding time was only slightly increased. The experiments of Duke (77) on the rate of regeneration

[34] References 44, 167, 203, and 219.

[35] References 63, 166, 203, and 217.

of platelets also showed in effect that when the fibrinogen content of the plasma was diminished at the same time as the number of platelets a marked tendency to haemorrhage existed. However, alteration in the coagulability of the blood-plasma is not all-important in bringing about change in the duration of bleeding time, for although increase in the coagulation time may be associated with increase in bleeding time in the presence of an increase or decrease in the platelet count it is more frequently found without a corresponding increase in bleeding time. Further, coagulation time may be normal and the bleeding time increased. I found cases to illustrate all these points.

In earlier work with anti-platelet serum, benzol, diphtheria toxin, and X-rays it was difficult to exclude the possibility that in addition to reducing the platelet count the endothelium of the capillary vessels was also damaged. More recently it has been demonstrated that, after intravenous injection of gelatine, a marked reduction in the number of platelets may be associated with only a very slight increase in the duration of bleeding time (195). Bedson (34) found that the platelet count could be considerably reduced without the occurrence of haemorrhage unless the endothelium of the capillary vessels was damaged. Wittkower [36] also, by means of X-rays, found that no haemorrhage resulted when the platelets numbered only 19,700. These experimental results confirm the clinical observations that a diminished platelet count may exist without the appearance of haemorrhage or without any increase in the duration of bleeding time. On the other hand, Pulvertaft (186) has shown that without any diminution in the platelet count the clinical picture of purpura fulminans may be simulated when streptococcal toxin is injected into rabbits, the lesion being due to damage to the capillary endothelium.

From a consideration of all the clinical and experimental evidence it is very doubtful if the platelet plays the part assigned to it by Duke and others.[37] It is also questionable if the thrombocytopenia which is frequently found in purpura haemorrhagica, pernicious anaemia, and acute leukaemia is the cause of the haemorrhagic symptoms and the prolongation of bleeding time. The coagulation time is usually normal in these diseases, therefore it is unlikely that the plasma is at fault. It can only be concluded that the lesion exists in the walls of the capillary vessels. This conclusion is the natural outcome of the knowledge that bleeding time may be prolonged when the platelets are normal or increased in number, and that a marked reduction in the platelet count may exist without any increase in the bleeding time or the appearance of spontaneous haemorrhage. It is further justified by the knowledge that the duration of bleeding time varies with the site of puncture. The variations which have been observed can only be explained on the basis that the capillaries are able to modify bleeding time.

According to Krogh (129) alteration in the capillary diameter is effected by contractile cells—the Rouget cells—which encircle the wall by means of

[36] Cited from Leschke and Wittkower (149).

[37] References 70, 78, 79, 94, 95, 112, and 124.

prolongations of their cell-body protoplasm. Aschoff (17) is unwilling to admit the contractile function of the Rouget cells, and apparently there is doubt in the minds of others as to the function of these cells (151). Although there is some doubt as to the mechanism whereby alteration in the capillary diameter is effected it seems to be admitted that the capillary walls have the power of independent contraction and relaxation. It is obvious, therefore, that the time taken to close a puncture wound will depend on the integrity of the capillary wall. It is also obvious that the amount of bleeding will vary according to the state of contraction and relaxation of the capillaries as determined by the temperature of the skin and the surrounding atmosphere, and possibly to some extent on the arterial blood-pressure. It has been shown experimentally that bleeding time can be modified by adrenalin, pituitrin, amyl nitrite, and emetine, all of which substances act through the medium of the capillaries (216). The active process of capillary contraction is, in health, the normal mode of reaction to injury. In the presence of this mechanism it is difficult to understand why platelets should be necessary to 'plug' potential spaces. Moreover, when contraction does occur, it is likely that 'plasma skimming' takes place, with the result that plasma only has access to the wounded capillary vessels, the red and white cells and probably the platelets being excluded. Eberth and Schimmelbusch (84) were struck by the fact that even when a vessel was pierced by a needle the platelets did not adhere to the injured wall unless the speed of the blood-stream was diminished.

In disease the capillary endothelium may be so weakened or damaged by toxins or nutritive disturbance that this reaction to injury is modified. When the distribution of many of the skin eruptions in disease is considered it is quite reasonable to expect that the degree of capillary weakness or damage would vary throughout the body, with the result that, other conditions being equal, the duration of bleeding time would vary with the site of puncture. Such variations would be unlikely if bleeding time depended on the number of platelets in the circulation. It is conceivable also that according to the nature of the disease the type of capillary abnormality will be different and thus give rise to different purpuric manifestations. Thus there is the type in which bleeding takes place into a papule, blister, or the lesion of an exanthematous rash, the type met with in scurvy or the frankly toxic states, or that which gives rise to the haemorrhagic signs peculiar to purpura haemorrhagica, pernicious anaemia, and acute leukaemia. With regard to purpura haemorrhagica Leschke [38] noted that capillary contraction was delayed, absent, or diminished in intensity. Bermuth,[38] however, observed normal capillary response in this disease. In all their cases of purpura haemorrhagica Leschke and Wittkower (149) found endothelial cells in the blood, a finding which they regarded as a sign of increased vulnerability of the capillary walls.

A test which is thought to indicate capillary weakness is the 'capillary resistance test' of Hess (116). In this test the circulation of the arm is restricted,

[38] Cited from Leschke and Wittkower (149).

and, where capillary weakness exists, it is claimed that petechiae or larger skin haemorrhages appear after restriction is removed. Frank (96) noted that petechial haemorrhages appeared and became more marked as the platelets diminished progressively below 75,000. In two of my cases no skin haemorrhages were observed when the platelets numbered 14,000 and 45,000. In another case, however, petechiae were observed when the platelets numbered 115,000. Other writers obtained negative results when the platelets were diminished (47, 94), for example at 6,000 (116), and positive results when the platelets were present in normal numbers (116, 196). The result of the test is therefore not dependent on the number of blood-platelets. Its reliability as a guide to capillary weakness is also doubtful, as it may be negative in the presence of extensive skin haemorrhages, as shown by one of my cases of purpura haemorrhagica. Clopton (43) also reports a similar finding. The test is not therefore of any great practical value, although a positive result would certainly indicate vascular abnormality. In all four cases of purpura haemorrhagica investigated by me it was negative, but in one of the cases of pernicious anaemia and the case of acute leukaemia a positive result was occasionally obtained.

It is evident that the problem of the cause of the spontaneous haemorrhages and increased bleeding time in thrombocytopenic conditions is one of great complexity. In such conditions alteration in the coagulability of the plasma does not commonly occur, therefore the cause of haemorrhage must be ascribed either to diminution in the platelet count or to vascular abnormality. The constancy with which thrombocytopenia is associated with bleeding makes it difficult to exclude altogether the possibility that reduction in the platelet count is in part responsible for spontaneous haemorrhage. However, in view of the evidence, clinical and experimental, that bleeding time may be prolonged when the platelets are normal or increased in number, or that it may vary within healthy limits in the presence of thrombocytopenia, it seems to me that the all-important factor in controlling capillary haemorrhage is not the number of blood-platelets but the ability of the capillary vessels to contract. I think that the thrombocytopenia so often associated with purpuric haemorrhage is merely a coincident phenomenon. According to this view purpura haemorrhagica is due to defect in the capillary walls.

Blood-platelets and Anaphylaxis.

Achard and Aynaud [39] found that when peptone was injected into the circulation the platelets agglutinated and collected in the liver capillaries. In sensitized anaphylactic dogs they observed that the tendency to agglutinate was much increased. Lee and Vincent (135) noted that on producing experimental anaphylaxis a diminution occurred in the number of circulating platelets. This agglutination of platelets has been thought to cause the severe

[39] References 10, 11, and 12.

symptoms of anaphylaxis. Pesci[40] believed that agglutination of platelets in the capillaries of the brain brought about thrombosis and flocculation of plasma colloids. Pardi (170) did not find any platelets in the brains of anaphylactic animals, but he found large numbers in the blood-vessels of the liver, lungs, and spleen, and he thought that thrombotic masses of platelets in these viscera caused the phenomena of anaphylaxis.

On the other hand, it has been thought that anaphylaxis was due to toxic substances liberated from platelets.[41] It has been shown that the constricting action of serum on a ring of artery isolated from the sheep (122) was due to platelet substances (206), and that aqueous extracts of platelets from the rabbit and horse, but not the dog, brought about constriction of an arterial ring isolated from the dog (148, 195). However, serum from rabbit plasma rich in platelets, when injected intravenously into rabbits, produced a fall in blood-pressure (145), and a similar effect resulted when aqueous extract of rabbit platelets was injected into the rabbit or dog (146, 195). Platelet extracts of man and dog did not influence the blood-pressure of rabbits or dogs (146, 195).

To explain these contradictory results Klecki and Pelczar (126) thought that the platelets liberated two substances having opposite actions. Roskam (195) suggested that the platelet extract acted like histamine by constricting the arteries and veins and dilating the capillaries. In the case of platelets of man and dog he thought that an equilibrium was established between the vaso-constrictor and vaso-dilator actions, and that liberation of platelet substances determined the fall in blood-pressure in anaphylactic shock. In the case of the human being and the dog he suggested that the action was localized to the capillaries of the viscera in which the platelets were agglutinated. Roskam admitted, however, that there was no reason to suppose that the aqueous extract of platelets was similar in composition to any substance liberated by living platelets. He pointed out that if the active substance present in the aqueous extract was histamine then it would be likely that the platelet contained it in common with many other cells of the body. Apart from this criticism, it had already been shown by Achard and Aynaud that in the state of anaphylaxis the platelets were not destroyed (5, 7). In addition, Zunz and Goværts (225, 226) found that all the phenomena of anaphylaxis could be produced in the absence of platelets. Klecki and Pelczar (126) showed that increase in the platelet count did not influence the course of anaphylaxis and that excess of platelet substance in the circulation did not produce anaphylactic shock.

It must be concluded that neither brisk agglutination nor destruction of platelets with liberation of toxic substances produces anaphylaxis. It is likely that agglutination of platelets is not the cause but merely one of the effects of the state of anaphylaxis.

[40] Cited from Klecki and Pelczar (126).

[41] Zeller; Freund; cited from Klecki and Pelczar (126).

Summary and Conclusions.

The blood-platelet is present in human blood as a definite morphological element. In health it is a non-nucleated, round or oval, disk-like body, having an average diameter of 2 or 3 microns and a hyaline cytoplasm containing numerous granules.

It has its independent origin in the bone-marrow and probably arises from the megakaryocyte.

Effete platelets are destroyed in the spleen by the cells of the reticulo-endothelial system.

In health the number of platelets in the blood of man varies constantly between 250,000 and 450,000 per c.mm.

In disease the platelet count varies between much wider limits. It is diminished in acute myeloblastic leukaemia, splenic anaemia, malignant endocarditis, pernicious anaemia (relapse), acute tonsillitis, lobar pneumonia (pre-critical phase), and pyaemia. The count is normal or only slightly diminished in Henoch-Schönlein and static purpura, in scurvy, haemophilia, acholuric jaundice, diabetes mellitus, pelvic sepsis, and hyperthyroidism, while in chronic myeloid leukaemia, secondary anaemias, lobar pneumonia (convalescence), acute rheumatism, nephritis, malignant disease, and chronic forms of tuberculosis the platelet numbers are normal or increased. In purpura haemorrhagica and polycythaemia vera the counts may be diminished or increased.

When the platelets are markedly reduced in number there is variation in size with a relative increase in the number of the smaller forms. In addition there is a varying degree of basophilic staining of the cytoplasm with irregular distribution in the granular content. When the count is high, or when the platelets are rapidly increasing in number, they tend to be larger and less granular. In the period of rapid increase basophilia is common. Basophilia of the platelet cytoplasm indicates immaturity.

The abnormalities in size, granulation, and staining reaction of the platelets described by others as peculiar to purpura haemorrhagica have been found in the blood in other pathological states. The haemorrhages characteristic of purpura haemorrhagica are not due to inherent defects in the blood-platelets as determined by morphology.

In acute myeloblastic leukaemia, chronic myeloid leukaemia, and polycythaemia vera the platelet count depends on the degree of hyperplasia of the leucopoietic or erythropoietic tissues. In pernicious anaemia and splenic anaemia the platelet-forming tissue is affected in common with the other haemopoietic tissues.

Loss of blood is followed by an increase in the platelet count. This increase is a regenerative process and reflects the state of activity in the blood-forming tissues.

The platelet count is reduced in the acute phase of some illnesses and increased in convalescence. No reduction in the count was observed in the

acute phase of rheumatic fever. The diminution in the platelet numbers found in acute infections is due to toxic action on the platelet-forming tissues, and the increase of convalescence is a sign of increased haemopoietic activity.

Diminution in the platelet count in purpura haemorrhagica is due to 'toxic' inhibition of normal platelet formation and not to excessive destruction of platelets.

The effect of X-rays on the platelet count varies with the patient, the disease, and the dosage given.

Phenylhydrazine hydrochloride produces an increase in the number of platelets which is merely an expression of haemopoietic activity.

When patients suffering from pernicious anaemia are fed with liver the platelets become increased in number.

Splenectomy is followed by an increase in the platelet count.

The number of platelets in the circulation is no guide to the rapidity with which coagulation occurs. Clotting of blood depends primarily on the plasma and the influence of the platelet is of minor importance.

Increase in the number of platelets does not induce thrombosis.

Retraction of the clot is not proportional to the number of platelets in the blood. It depends on (*a*) the blood-plasma and (*b*) the blood-platelets. The former is the more important.

Thrombocytopenia may be present in the absence of spontaneous capillary haemorrhage or prolongation of bleeding time. Spontaneous capillary haemorrhage and prolongation of bleeding time may exist in the presence of platelets in increased numbers. Bleeding time varies within wide limits when the platelets are constantly diminished. It also varies with the site of puncture.

The capillary resistance test is of doubtful value.

The most important factor in controlling spontaneous capillary haemorrhage or duration of bleeding time is not the number of blood-platelets in the circulation but the ability of the vessel wall to contract. The haemorrhages of purpura haemorrhagica are due to defect in the capillary walls.

Blood-platelets are not responsible for the phenomena observed in anaphylactic shock.

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616.1—008.615

SOME OBSERVATIONS ON THE CIRCULATORY MECHANISM IN MARATHON RUNNERS[1]

By CRIGHTON BRAMWELL and REGINALD ELLIS

With Plates 19 and 20

The observations on which this paper is based were made at the last Olympic Games at Amsterdam, where, at the invitation of our Dutch colleagues, we were working as members of a team organized by Prof. Buytendijk of Gröningen. We examined altogether over 200 athletes, including runners, weight-lifters, swimmers, wrestlers, and competitors in various other events. Of these, the runners are the most interesting group to the cardiologist. They may be subdivided into four classes: (i) Sprinters—100 and 200 metres; (ii) Middle distance—400 and 800 metres; (iii) Long distance—1,500 to 10,000 metres; (iv) Marathon—42 kilometres.

1. *Physical Characteristics.*

It is interesting to compare these different groups.

Table I.

	No.	Age.	Weight kg.	Pulse-rate.	Blood-pressure.
Sprinters	18	22	65	66	116/77
Middle distance	16	23	65	63	119/81
Long distance	15	24	64	61	116/75
Marathon	28	27	60	58	123/78

In Table I, in the first column is given the number of men examined; in the second and third columns the average age and weight in each group; in the fourth column the average resting pulse-rate; and in the last column the average blood-pressure readings. The weight and blood-pressure readings in the first three groups are very similar; but the men who run the longer distances are slightly older and tend to have a rather lower pulse-rate.

When we come to the Marathon group we encounter something quite different. The clinical findings in the twenty-eight Marathon runners whom we examined during the period of training are given in Table II.

[1] Received November 26, 1930.

TABLE II. *Marathon Runners.*

Examined before Race.

Case No.	Age.	Weight kg.	Lowest pulse-rate.	Blood-pressure. Syst.	Blood-pressure. Diast.	Pulse-pressure.	Place.
339	21	52	52	110	65	45	—
365	25	51	53	110	60	50	—
444	27	66	48	105	65	40	—
445	37	63	51	120	80	40	14
446	28	58	48	135	90	45	7
447	30	68	51	120	80	40	15
448	22	50	47	120	80	40	—
478	25	58	52	120	80	40	4
482	20	53	60	115	90	25	6
500	25	51	62	110	75	35	—
607	39	69	59	145	85	60	—
635	25	62	50	115	65	50	—
646	26	54	60	130	85	45	—
650	32	50	61	120	80	40	—
655	27	56	70	145	70	75	—
658	22	54	58	130	70	60	—
692	20	61	52	110	75	35	—
717	27	67	66	115	70	45	—
718	32	67	65	140	90	50	—
720	31	66	60	105	70	35	3
722	33	61	47	115	80	35	12
736	28	64	67	145	95	50	—
822	27	60	62	115	75	40	—
824	27	68	53	145	90	55	—
862	31	51	70	130	85	45	—
871	20	63	70	110	75	35	—
974	29	57	53	115	75	40	—
994	27	71	56	135	90	45	2
Average	27	60	58	123	78	45	—

They are much older men, in the late twenties or early thirties. There was only one competitor under the age of 25 who did well in this race. Young men seem to lack the necessary stamina for feats demanding such great endurance. One finds the same is true of other prolonged physical efforts, as, for example, Arctic exploring. In Nansen's (12) expedition to the North Pole the average age of his twelve companions was 33; only three of them were under 30, and none under 25.

Whether the greater stamina of the older men is due to a nervous, a circulatory, or a metabolic factor it is difficult to say. But whichever be the case, the fact remains that men over 25 appear to be better fitted to run the Marathon than younger athletes.

This relation between age and long distance running cannot be disregarded when considering the question as to whether it is advisable to allow growing boys to compete in long distance cross country races. The possibility of the heart being damaged by such a prolonged strain merits serious consideration. The orthodox view of physiologists appears to be that a healthy heart is not likely to suffer damage from physical exertion, however severe. It is not the weakest link in the chain; something else will snap first. Amongst clinicians of long experience, however, opinions in this matter are less unanimous. Most

healthy schoolboys, it is true, run little risk of damage from over-exertion, for they stop before they are exhausted; but it is a well-known fact that there is a type of boy who runs himself to a standstill. It is he who causes the school medical officer anxiety, for he lacks the safety valve that protects his less determined companions. If one could with certainty exclude boys of this type there would be little danger in allowing the others to compete; but to pick them out is no easy matter. Hence, for their benefit, the cautious physician may be tempted to place a ban on such severe exertion, although he is fully prepared to admit that in the majority of instances—for the type of boy who gives up before he is completely 'run out' is much the more common—such caution is unnecessary.

In the Marathon, in addition to stamina, probably there is another factor in favour of the older man. His joints are rather less supple. Consequently he expends less energy in limiting their movements, and runs more economically. The very reverse is true of the sprinter: extreme suppleness is one of his most important assets—an asset which is the perquisite of youth.

Apart from the difference in age, the Marathon runner is of lighter build, his resting pulse-rate is lower, and his systolic blood-pressure rather higher than that of the runners in the other three groups.

The sprinter is of much less interest to the cardiologist. His chance of success depends more on perfect neuro-muscular co-ordination. He can run 100 metres without taking a single breath, and can trust to the buffering mechanism in his blood and muscles to deal, for the moment, with all the lactic acid produced. So far as the immediate requirements of his muscles are concerned he might almost dispense with his heart. For the longer distances, on the other hand, the efficiency of the circulatory mechanism is all-important, the long distance runner being dependent on the amount of oxygen he can obtain during the race.

2. *Oxygen Requirements.*

Oxygen debt. Muscular contraction is a strictly anaerobic process, depending on the energy liberated when glycogen is converted into lactic acid. The lactic acid produced is disposed of partly by oxidation to carbon dioxide and partly by reconversion into glycogen. This 'recovery process', unlike contraction, is essentially dependent on an adequate oxygen supply. During exercise, other than that of the briefest duration, the contraction and recovery processes of breakdown and repair are taking place concurrently; and as long as the removal of lactic acid keeps pace with its production an equilibrium is established and exercise can proceed. As soon, however, as the oxygen supply falls short of the requirements of the active muscles, lactic acid begins to accumulate in the tissues, and, as A. V. Hill and his co-workers (10) have expressed it, the body 'goes into debt' for oxygen. The panting after a race supplies the excess of oxygen necessary to pay off this debt and to provide for

the removal of the lactic acid which has accumulated in the body during the race. The extent of the oxygen debt is limited by the fact that when the concentration of lactic acid in the muscles reaches a certain value (about 0·3 per cent.) 'fatigue' sets in, and the muscles, for the time being, become incapable of further contraction. Whereas the 100 metre sprinter can rely entirely on his oxygen credit, the long distance runner depends on what his respiratory and circulatory mechanisms can provide during the race.

A. V. Hill and his co-workers determined by direct experiment the maximum oxygen debt and the maximum oxygen intake. They found that in a man of 70 kilos the former is about 16 litres and the latter about 4 litres per minute. From these two figures we can calculate the total quantity of oxygen available during any given period of time.

TABLE III.

Duration of race (mins.).	Oxygen available (litres).			
	Credit.	Income.	Total.	Per min.
1	16	4	20	20
30	16	120	136	4·5

In Table III two races are compared, the one lasting one minute and the other half an hour. If one assumes that both men are completely 'run out' at the finish (i. e. that they have exhausted their oxygen credit) then the man in the long race will have been able to draw on his oxygen credit only to the extent of half a litre per minute, as compared with 16 litres in the case of the man who runs the shorter distance.

Hill (9) further calculated the oxygen requirement for running at different rates by measuring the total quantity of oxygen consumed during the subsequent process of recovery. He was able to show that the quantity of oxygen available per minute is in itself sufficient to determine the speed at which it is possible to run different distances. He found that the theoretical times calculated from oxygen credit and oxygen income are just a trifle shorter than the actual world's records for the various distances.

The long distance runner who runs with perfect judgement saves the greater part of his oxygen credit for his final sprint. In the earlier part of the race he runs by the clock. Some expert long distance runners look at their watches as they complete each lap, and regulate their pace accordingly.

At Amsterdam we were struck by the fact that, after the race, many of the competitors in the 10,000 metres were much more 'done' than the Marathon runners. The reason for this no doubt is that, to get a place, the long distance man has to exhaust his oxygen credit in the final sprint, whereas the Marathon runners are so strung out by the end of the race that they can hardly hope to catch up the man in front. A final sprint would be of no avail, and they are content to jog along to the tape at a rate which they can meet out of oxygen income.

3. *Glycogen Balance.*

In addition to circulatory efficiency the Marathon runner has another problem to contend with, a problem which does not concern any of the other groups of athletes. He is like a man who flies the Atlantic in an aeroplane. It is a question whether his fuel will hold out. The fuel of the muscles is glycogen, and it is possible to make a rough computation of the amount of glycogen required to run the Marathon. The race takes about 2½ hours. Supposing the athlete's average oxygen intake over this period is 3 litres per minute, his total oxygen consumption will then be 450 litres. This would yield 2,250 calories, which implies the oxidation of approximately 550 grm. of glycogen. On the credit side of the account we have the glycogen available in the liver and muscles. Taking the weight of the liver as 1,500 grm. and assuming that it contains 15 per cent. by weight of glycogen, we get a total yield of 225 grm. The muscles of a man constitute about 40 per cent. of his body weight. Taking their percentage of glycogen as 1·5, the total yield from this source, in a man of 60 kilos, would be 360 grm. So the glycogen balance sheet in the Marathon runner will read somewhat as follows:—

TABLE IV. *Glycogen Balance Sheet.*

Probable Liabilities.	Grm.	*Probable Assets.*	Grm.
O_2 consumption 2½ hours at 3 litres per min. = 450 litres. Equivalent to glycogen	560	Muscle glycogen 24 kilos at 1·5 % .	360
Credit balance	25	Liver glycogen 1,500 grm. at 15 % .	225
	585		585

In this calculation we have probably erred in favour of the credit side, for it is more than likely that the oxygen intake is higher than 3 litres per minute, and that the glycogen in the muscles and liver is less than 1·5 and 15 per cent. respectively. If that be so, we shall be faced with a debit balance, and forced to conclude that the muscles are burning fat as well as glycogen. But, even if our estimate be accurate, it is clear that the Marathon runner is coming dangerously near the verge of bankruptcy. That such is actually the case is shown by the blood-sugar analyses made by our colleague Dr. C. H. Best (3). In two of the athletes whom we examined after the race, Best (to whom we are indebted for these figures) found blood-sugar values of 0·055 and 0·053 per cent. respectively.

These two men were on the verge of hypoglycaemic convulsions. On the day of the Marathon at Amsterdam the weather was cool, but when the Marathon is run under less favourable conditions some of the competitors do actually develop symptoms of acute hypoglycaemia. Both these men were profoundly exhausted and appeared very weak. The one was deeply cyanosed, he showed inco-ordination of his muscular movements, and his blood-pressure, which

before the race had been 110/60, had fallen to 85/40, the lowest value recorded in any of the men whom we examined. The other man was only moderately cyanosed. He finished ninth, and his blood-pressure after the race was 105/75. Unfortunately we did not have the opportunity of examining him before the race. None of the Marathon runners we examined whose blood-sugar values were normal after the race showed cyanosis, and most of them appeared to be in surprisingly good condition. For the sake of comparison, in the lower half of

TABLE V.

Place.	Blood-sugar.	Blood-pressure.		Clinical notes.
		Before.	After.	
9	0·053	—	105/75	Cyanosed. Very weak
—	0·055	110/60	85/40	Very cyanosed. Profoundly exhausted. Muscular inco-ordination
4	0·092	120/80	110/70	Good condition
6	0·091	115/90	105/60	Good condition

Table V we have given the blood-sugar and the blood-pressure values of the two Japs who finished fourth and sixth. These findings tempt one to suggest that the circulatory failure responsible for cyanosis may be the result of a shortage of glycogen in the heart muscle. A natural consequence of the shortage of glycogen is that the Marathon runner is ravenously hungry at the end of the race.

Ingestion of sugar, &c. With the object of increasing the body's store of glycogen it is customary to feed long-distance runners on large quantities of sugar before the race. One of our friends, who is an expert long-distance runner, tells us that he takes twelve lumps of cane sugar every two hours for twelve hours before a long race, amounting in all to about ¾ lb. He considers that he derives distinct benefit from so doing.

TABLE VI. *Food taken Before and During Race.*

Ref. no.	Nationality.	Place.	Blood-sugar after race (%).	Food taken (Race started 3 p.m.).
365	Mexico	—	0·055	Meat and eggs at 11 a.m. Cocoa during run
448	Holland	—	0·100	Bread and cocoa at 12 noon. One egg during run
478	Japan	4	0·092	Rice and melon at 12.30. Lemonade with added sucrose during run
482	Japan	6	0·091	Moderate meal of rice at 12 noon. Lemonade with added sucrose during run
P/521	U.S.A.	—	0·099	Meat and potatoes at 11.30 a.m. One glass of milk during run
P/547	U.S.A.	9	0·053	Meat and eggs at 11.30 a.m. Small part of an orange just after finish about 5 min. before blood-sugar sample taken

The Marathon runners are allowed to stop for refreshment at certain

specified places en route, and most of them avail themselves of this privilege. The amount of sugar they could consume in this way is, however, hardly sufficient to have any appreciable effect on the total available glycogen. The examples given in Table VI serve to illustrate the diversity of taste and diet amongst some of the men whom we examined.

Another substance which has been used more or less empirically in the feeding of athletes is sodium phosphate. A possible explanation of its value is afforded by recent biochemical work, which has shown that hexose phosphate is an intermediate product in the breakdown of glycogen to lactic acid. In this connexion it is interesting to note that sodium phosphate was at one time a favourite drug for the treatment of exophthalmic goitre (4), in which condition the raised metabolic rate makes a heavy demand on the carbohydrate metabolism, and in this respect renders the patient comparable to an athlete who indulges in prolonged and severe physical exertion.

4. *Cardiac Enlargement.*

The heart ratio. Before considering the vexed question of cardiac enlargement in athletes it is instructive to pass for a moment from man to the lower animals. In Table VII, which is taken from Clark's book (5), the heart-weight in various animals is expressed as a percentage of the body-weight. This gives a figure which is generally spoken of as the 'heart ratio'.

TABLE VII. (*Clark*).

Animals with High Heart Ratios.		*Animals with Low Heart Ratios.*	
Animal.	Heart ratio.	Animal.	Heart ratio.
Deer	1·15	Rabbit (wild)	0·27
Badger	1·08	„ (tame)	0·3
Wolf	1·017	Field vole	0·37
Weasel	0·939	Hedgehog	0·38
Stoat	0·94	Wild boar	0·39
Fox	0·92	Norwegian rat	0·4
Seal	0·92	Sheep (domestic)	0·42
Red deer	0·90	Guinea-pig	0·42
Hare	0·77	Domestic cat	0·46
Dog	0·85	„ ox	0·49

Clark points out that, if one excludes the smallest mammals, all of which have a high heart ratio on account of their high metabolic rate, the remainder of the mammalian group may be divided into two classes, namely, those which are, and those which are not, capable of *continuous and severe muscular exertion.* In the former the heart ratio is found to be higher than in the latter. Or again, comparing birds or mammals of the same or similar species, one finds that the athletic members have much higher heart ratios than their more sedentary relations. This is shown in Table VIII.

TABLE VIII (*Clark*).

Inactive Animals.	Body-weight grm.	Heart ratio.	*Active Animals.*	Body-weight grm.	Heart ratio.
Barndoor cock . .	1336	0·68	Game cock . . .	1663	1·03
Tame duck . . .	2060	0·63	Wild duck . . .	770	1·06
„ rabbit . . .	2000	0·24	Hare	4000	0·77

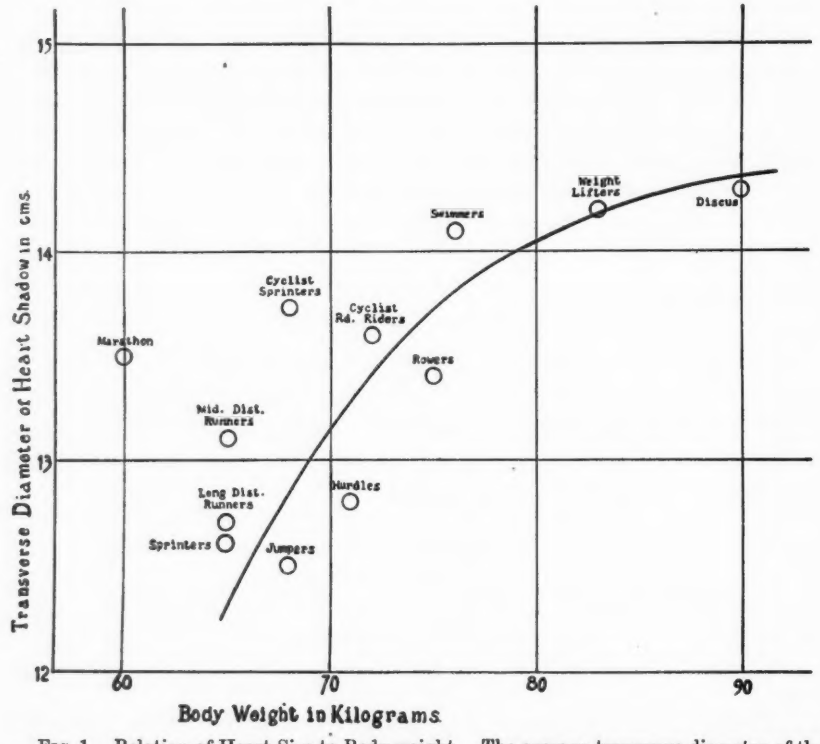

FIG. 1. Relation of Heart Size to Body-weight. The average transverse diameter of the heart shadow in centimetres is plotted against the average body-weight in kilograms, in the case of each group of athletes examined. With the exception of the Marathon runners the co-ordinates of most of the groups lie in fairly close proximity to a mean curve.

Heart size in Olympic athletes. The X-ray measurements of heart size in the athletes whom we examined were made by our colleague Dr. Herxheimer of Berlin, to whom we are indebted for these values. His figures show that, comparing the four groups of runners (Table IX), the Marathon runners have the biggest hearts. This is all the more striking, since they are the smallest men. In Fig. 1 the relation of heart-weight to body-weight in all the different groups of athletes we examined is represented graphically. Most of the points lie in fairly close proximity to a mean curve. There is, however, one striking exception, namely, the Marathon group, whose hearts are relatively much bigger than those of the other athletes.

TABLE IX. *Runners.*

	No. examined.	Average heart diameter. cm.	Average weight kg.
Marathon . .	32	13·5	60
Long distance .	16	12·7	65
Middle distance .	16	13·1	65
Sprint . . .	18	12·6	65
Hurdles . . .	6	12·8	71

If, instead of comparing average values, we consider individual cases we find that amongst Marathon runners the percentage of very large hearts is surprisingly high. The transverse diameter of the heart shadow was found to exceed 15 cm. in eighteen of the 192 athletes we examined, and it is convenient to take this value as an arbitrary dividing line between 'big' and 'very big' hearts. The particulars of the eighteen men with very big hearts are given in Table X. For the sake of comparison the average heart size and the average body-weight in each of the groups in question is given.

TABLE X. *Incidence of Very Large Hearts.*

	A. Transverse diameter over 15 cm.		B. Whole group (all sizes).		
Event.	No.	Average weight kg.	No.	Average diameter.	Average weight kg.
Cyclists	5	74	22	13·7	65
Weight-lifters	4	94	15	14·2	83
Discus-throwers	3	90	6	14·8	91
Marathon	3	65	32	13·5	60
Other runners	1	75	50	—	—
Other events*	2	68	67	—	—
Total	18	—	192	—	—

* Other events include:—hurdlers 6, boxers 16, swimmers 6, rowers 9, fencers 5, wrestlers 9, jumpers 13, decathlon 3.

That there should be a high percentage of very big hearts amongst discus-throwers and weight-lifters is not surprising, for they are big men, but the high percentage amongst cyclists and Marathon runners cannot be accounted for in this way. Especially is this the case when one considers the average weight of the three Marathon runners who had very big hearts was only 65 kilos. All three did creditably in the race. They finished second, twelfth, and seventeenth respectively. Amongst the other fifty runners there is only one very large heart. Unfortunately we did not have the opportunity of examining either of the champion long distance runners Nurmi or Ritola.

Our finding of cardiac enlargement in Marathon runners agrees with that of most previous workers, though some have reported otherwise. Gordon (7), for example, in a similar series of observations on American Marathon runners, found that even the largest hearts fell well within the limits of normal variation. Herxheimer (8), on the contrary, as the result of a previous series of

observations, came to the conclusion that the heart is enlarged in men who participate in all sports entailing prolonged exertion, such as Marathon runs, ski-ing, cycling, and rowing. Deutsch and Kauf (6), in studying the question of cardiac enlargement in athletes, came to the conclusion that it was most prone to occur in oarsmen, cyclists, and ski runners.

In 1926 Ackermann (1) published a series of X-ray measurements of the transverse diameter of the heart in twenty-six German Marathon runners before and after a race. His figures indicate that in most cases the heart size is from 4 to 12 mm. smaller after the race. He also made similar measurements on nine competitors who had to give up, owing to exhaustion, before reaching the tape. In this group the percentage of cases of dilatation is very much higher. A summary of the two groups is given for comparison in Table XI. Whereas, in those who finished, eighteen showed a diminution and six[2] an increase in heart size, in those who had to give up three only showed a diminution and the other six an increase, a ratio of 1 : 2 instead of 3 : 1.

TABLE XI. (*Ackermann Summary*).

Change in Tranverse Diameter of Heart Shadow after Marathon.

	Finished.	Gave up.
Increase	6	6
No change	2	—
Decrease	18	3

Unfortunately the problem is not so simple as it appears at first sight. Vaquez and Bordet (15) have drawn attention to a possible fallacy. They point out that the diminution in the transverse diameter of the heart shadow found after a race may be due to a change in the position of the diaphragm. They maintain that when an athlete, who is still suffering from hyperpnoea after a race, is told to hold his breath, he tends to stop breathing in full inspiration. Consequently the diaphragm is depressed below the 'neutral' position, which it assumes when the breath is held during normal quiet respiration, and the transverse diameter of the heart shadow is correspondingly diminished. Vaquez and Bordet further assert that when an athlete is completely exhausted he can hold his breath most easily in the position of full expiration, and that the apparent increase in size of the heart in these cases is due, in part at least, to the high level of the diaphragm.

Heart-weight in man. All the figures relating to heart size in the Olympic athletes whom we studied are based on measurements of the *transverse diameter* of the heart shadow. What we should really like to be able to do is to ascertain the *weight* of the heart. That the transverse diameter of the heart shadow is not necessarily a reliable guide to the actual size of the organ is unfortunately true, for radiograms of the chest show that the anatomical disposition of the heart in the thorax is subject to considerable variation. The two extremes are

[2] Two cases in which the change was only 1 mm. are not included, for this value is within the limits of error of measurement.

the vertical and the transversely disposed heart. It is obvious that, in extreme cases such as these, a measurement of the transverse diameter alone will give an entirely false impression of the relative weights of the two hearts.

Elaborate mathematical formulae have been suggested for calculating the heart-weight from the transverse diameter of the heart shadow, but most of these suffer from the same fundamental defect—that they are based on a single measurement in one plane.

The assessment of heart size is a much more complicated problem. The surface area of the heart shadow would be more reliable, but even this could not be expected to yield more than a rough approximation of the true figure. While admitting the fact that the transverse diameter of the heart shadow may in certain cases give a misleading impression as to the size of the organ, owing to individual variations in the lie of the heart, nevertheless we believe that the figures which we have given in this paper are worth something; because we have been comparing *average values* in fairly large groups of athletes, and not individual cases. When the average values in two groups differ so widely as they do in the case of the Marathon runners and sprinters, for example, one is bound to conclude that the hearts in the one group are definitely larger than those in the other.

There is a second valid criticism which must be met in an investigation of this kind, namely the personal equation. The absolute values given by different radiologists vary considerably although the relative values in similar series of observations may be strictly comparable. This is largely due to differences in technique. We wish, therefore, to emphasize the fact that all the measurements to which we have referred in this paper were made by the same observer (one who has had a very wide experience in this particular branch of radiology), under strictly comparable conditions. The values here given were calculated from measurements on films taken with the tube at two metres distance from the screen, and have been further corrected for distortion at that distance by a deduction of five per cent.

These observations compel us to conclude that the hearts of Marathon runners are, as a rule, relatively bigger than those of most other athletes. It by no means follows, however, that cardiac enlargement in these men is in any sense pathological. The Marathon runner needs a big heart, and it is probable that his heart hypertrophies to some extent as the result of prolonged training. It seems to us, however, that there is another possible factor to consider. It may be that men who have hearts somewhat bigger than the average make the best Marathon runners. They start life with a natural advantage. If this be so, it is partly the fact that he is born with a big heart that makes a man a good Marathon runner, and his cardiac development is not solely a consequence of his training.

The term 'athletes' heart'—signifying an enlarged heart resulting from athletics—is still far too common in medical parlance. There is no doubt that a man who is not in training, or who is convalescing from some acute illness

such as influenza, may develop pathological dilatation as the result of some athletic exertion. We have referred above to the possibility of similar detrimental effects in growing boys. But surely the fact of being able to compete successfully in the Marathon is in itself sufficient evidence that a heart larger than normal is not necessarily diseased.

Predominance. We can go a step farther and endeavour to ascertain whether it is the right or the left heart which is involved in cases of enlargement, by seeking for evidence of right or left-sided preponderance in the electrocardiogram. In most of the athletes whom we examined at Amsterdam an electrocardiogram was taken by our colleague Dr. Hoogerwerf of Leiden. His records show right-sided ventricular preponderance in fifty-three, and left-sided preponderance in nineteen instances. It is interesting to compare the different groups of athletes in this respect. Table XII summarizes the results of these findings.

TABLE XII. *Ventricular Predominance.*

	Right.	Left.
Marathon	7	4
Other runners	19	1
Jumpers	4	1
Cyclists	7	6
Oarsmen	5	0
Weight-lifters	0	3
Other groups	11	4
Totals	53	19

The striking feature here is that amongst the runners, with the exception of the Marathon runners, left preponderance was found in one case only, whereas right preponderance is common. This finding is in accordance with the clinical observation that, in runners, it is the right and not the left heart which is prone to give way: for in them circulatory insufficiency usually manifests itself by cyanosis, dyspnoea, and venous engorgement.

Blood-Pressure.

In the various groups of athletes whom we examined, with the single exception of the weight-lifters, the average blood-pressure values were found to lie well within the normal limits of variation for young men. In the case of the runners the average systolic pressure varied in different groups from 116 to 123 mm. and the diastolic from 75 to 81 mm. As compared with non-athletic individuals, these values are a trifle on the low side. Alvarez (2) in a series of 2,930 undergraduates found an average systolic value of 126·5 mm.

In 19 cases only amongst the 192 athletes we examined was the systolic pressure above 135 mm. Seven of them were weight-lifters, and 5 were Marathon runners. The remaining 7 cases were distributed amongst 149 athletes of different types. The ages and weights of the 5 Marathon runners are given in Table XIII.

TABLE XIII. *Marathon Runners with Systolic Pressure over 130 mm.*

No.	Age.	Weight. kg.	Blood-pressure.	Place.
607	39	69	145/85	—
655	27	56	145/70	—
718	32	67	140/90	—
736	28	64	145/95	—
824	27	68	145/90	—
446	28	58	135/90	7
994	27	71	135/90	2

No. 736 was the only man in the whole group whose diastolic pressure was over 90 mm. Only two other men in the group of 28 (Nos. 446 and 994) had a systolic pressure over 130 mm. and both of these took good places in the race. It is noteworthy that all these men were over 26 years of age.

Immediately after the Marathon we had the opportunity of examining clinically nine of the competitors whom we had examined previously during the period of training. In Table XIV the pulse-rates and blood-pressure readings of these men before and after the race are compared. Although there is a considerable fall in both systolic and diastolic pressures, the pulse-pressure in most cases remains practically unchanged.

TABLE XIV. *Marathon Runners.*

Examined Before and After the Race.

			Pulse-rate.		Blood-pressure.					
					Syst.		Diast.		Pulse-pressure.	
No.	Age.	Place.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.
339	21	—	52	73	110	95	65	55	45	40
365	25	—	53	60	110	85	60	40	50	45
*448	22	—	47	96	120	90	80	50	40	45
478	25	4	52	91	120	110	80	70	40	40
482	20	6	60	90	115	105	90	60	25	45
500	25	—	62	76	110	90	75	65	35	25
692	20	—	52	91	110	100	75	60	35	40
824	27	—	53	80	145	120	90	65	55	55
974	29	—	53	84	115	100	75	80	40	20
Aver.	24	—	54	82	117	100	77	61	40	39

TABLE XV. *Marathon Runners.*

Examined After the Race.

Prog. No.	Age.	Place.	Pulse-rate.	Blood-pressures.		
				Syst.	Diast.	Pulse-pressure.
71	29	1	—	100	80	20
69	—	—	92	100	70	30
*521	40	—	70	95	75	20
547	34	9	89	105	75	30
Average	34	—	85	100	75	25

* Distinctly cyanosed after race.

In Table XV are given the clinical findings in four other Marathon runners examined immediately after the race. Unfortunately we did not have the

opportunity of examining these four men during the period of their training. Their average systolic pressure is the same as that of the previous group but the diastolic pressures are much higher and consequently the pulse-pressures are small.

It is difficult to reconcile these findings with those given in the previous table. Possibly this discrepancy may be explained by the difference in age in the two groups, the men in the second group being distinctly older than those in the first. In support of this hypothesis is the fact that there are only two instances of a low pulse-pressure in the first group, and both of these are in men over 25 years of age.

If we are correct in believing that the diastolic pressure is more stable in the older men this may be one factor in rendering them better fitted to undertake prolonged exertion.

In the case of aviators it has been found that men with a low pulse-pressure make the best pilots. In fact a high pulse-pressure is regarded with grave suspicion in medical examination of candidates for the Air Force.

Electrocardiographic Findings.

Amongst the 192 male athletes we examined the most interesting electrocardiographic findings were a prolongation of the '*P–R* interval', and certain modifications in the form of the *T* wave and *R–T* phase. The '*P–R* interval' exceeded 0·2 sec. in 17 cases. Five of these were Marathon runners, one being the man (No. 994) who gained second place in the race. In addition to a '*P–R* interval' of 0·24 sec. this man's record (Fig. 2) showed notching of the *P* waves, and a *T* wave which was of large amplitude in the first two leads and inverted in lead III. In one case (Fig. 3)—a 10,000 metre man, not a Marathon runner—partial heart-block with missed beats was present at the time of examination.

Notching of the *P* waves, similar to that so commonly found in cases of mitral stenosis, occurred in twenty of the athletes we examined; two only of these were Marathon runners.

T waves of abnormally large amplitude (Fig. 5) were found in nineteen records. Ten of these subjects were runners, five being Marathon runners.

In a series of electrocardiograms taken immediately after the Marathon, the *T* wave was generally found to be of smaller amplitude than in the records taken from the same subjects, prior to the race, but in other respects the auricular and ventricular complexes exhibited no obvious alteration.

Another curious modification in the form of a *T* wave was a high 'take off' (Fig. 5). This occurred in seven records, five of which were from middle or long distance runners. This feature is one which we had never previously seen in electrocardiograms taken from normal healthy subjects, nor do we know of its having been recorded in the literature. It reminds one of the ventricular

complex frequently seen during the process of recovery from myocardial infarction following coronary thrombosis, first described by Pardee (13).

Extra-systoles were observed in only three of the 192 male athletes we examined. One of these was a boxer with a heart-rate of 53, in whom the normal rhythm was interrupted by frequent extra-systoles of nodal origin. The other two athletes exhibited arrhythmia only after racing. The one was a cyclist sprinter in whom we found frequent extra-systoles after a trial race, his heart-rate at the time being 98 per minute. The other was the man who finished fourth in the Marathon. When we examined him immediately after the race, his heart's action was so irregular that clinically the condition might easily have been mistaken for auricular fibrillation. The electrocardiographic examination, however, showed that the arrhythmia was due to showers of extra-systoles.

Heart-Sounds.

A relative accentuation of the second heart-sound either in the region of the apex or at the base of the heart was of frequent occurrence.

In twelve of the 192 athletes we examined we were struck by a curious prolongation of the first heart-sound, not unlike the crescendo murmur of mitral stenosis. As we only had the opportunity of examining these men on one occasion and had no facilities for recording the heart-sounds graphically, we do not wish to over-emphasize this finding. Nevertheless, we feel that it was sufficiently striking to be worth mentioning. Of the twelve athletes in whom it occurred, three were Marathon runners, three were long distance runners, and three were cyclists. It was not present in any of the eighteen sprinters or sixteen middle-distance runners whom we examined.

In addition, in two of the Marathon runners we noted a definite reduplication of the first heart-sound at the apex, a peculiarity which we did not meet with in any other group of athletes. Finally, in several other Marathon runners in whom the first sound was neither reduplicated nor modified in the manner described above, it appeared to be definitely prolonged.

H. Sewell (14) has called attention to the fact that in the structurally normal heart, especially in cases of circulatory excitement, the first sound is frequently accentuated and may even have a crescendo character. He suggests that this may be explained by the fact that when the ventricle is filled at a certain rate the reflux of the blood current tends to bring the auriculo-ventricular valves into approximation. Under these circumstances, the auricle in contracting must force a channel between them and may cause vibrations of sufficient intensity to give rise to an audible presystolic murmur.

Successful Athletes.

Five out of the first seven places in the Marathon were taken by athletes whom we had examined during their training. Our findings in these five men are shown in Table XVI.

TABLE XVI. *Successful Marathon Runners.*

Examined Before Race.

No.	Place.	Age.	Weight.	Pulse-rate.	Blood-pressure.
994	2	27	*71*	56	135/90
720	3	31	66	60	*105/70*
478	4	25	58	52	120/80
482	6	*20*	53	60	115/90
446	7	30	58	*48*	135/90
Average		26·6	61	55	122/84
Average, whole group		27	60	58	123/78

The average values in this successful sub-group agree very closely with the average values of the Marathon group as a whole, but when we come to consider the individual members of the group this is far from being the case. No. 994, who finished second, is two kilos heavier than any of the other men in the group, and he has a relatively high blood-pressure (135/90), but a vital capacity of only 4·4 litres. He is not the build of a Marathon runner; he is too big. Nevertheless he finished only a few hundred yards behind the winner. The transverse diameter of his heart shadow measured 17·2 cm.: a value equalled in one instance only (a discus-thrower weighing 90 kilos) amongst the 192 athletes we examined. His electrocardiogram (Fig. 2), for which we are indebted to our colleague Dr. S. Hoogerwerf, affords evidence of delay in conduction from auricle to ventricle, his *P-R* interval (before the race) being 0·24 seconds. In the size of his heart, as well as in the form of his electrocardiogram, he differs almost as much from the 'normal' individual as does the latter from a patient suffering from heart disease. One is almost tempted to call him a cardiac superman.

No. 720, who finished third, has the highest vital capacity in the whole group (5·5 litres). No. 482, who finished sixth, is not only the youngest man in the group, but is five years younger than any other competitor who took a prominent part in the race. This is perhaps to be accounted for by the earlier maturity of the eastern races, he being Japanese. No. 446, who finished seventh, had a low pulse-rate and a fairly high blood-pressure (135/90). To sum up, four of these five athletes exhibited a striking divergence in one or more particulars from the average of the group.

Such discrepancies make one wonder what really are the essential attributes of a successful Marathon runner. They evidently include something more than a first-class circulatory mechanism. His heart, like the engine of the Atlantic airman, must be beyond reproach. But that alone is not sufficient; something more is necessary. Possibly that something is a metabolic factor related to the functions of the liver; or possibly it is, in part at least, a psychical factor which enables him to plod along heedless of the distractions which waste some of the energy of the more emotional competitors.

Many of the Marathon runners have a very phlegmatic temperament, and, during the course of our routine examination, we were struck by the fact that

their heart-rate is less susceptible to emotional and other disturbances than that of the other groups of athletes we examined. In each case we made two pulse counts, the one at the beginning and the other at the end of our examination. In the Marathon group these two counts were identical in five instances and differed by more than three beats in less than 50 per cent. of the men examined. In contrast with this we may take the group of sprinters. In not a single instance in this group were the two counts identical, and in five only did they differ by less than three beats.

TABLE XVII.

Difference in pulse counts.	Marathon.	Sprinters.
0	5	0
1–3 beats	11	5
More than 3 beats . .	12	13

Summary.

A group of twenty-eight Marathon runners was examined clinically, radiographically, and electrocardiographically during the final stage of training for the Olympic Games.

Compared with other Olympic runners they are older men, of a more phlegmatic temperament, generally of lighter build, and their resting heart-rate is slower.

The question of oxygen requirement, oxygen intake. and oxygen debt is discussed in relation to different types of running, and it is suggested that the smallness of their oxygen debt probably accounts for the absence of distress in many Marathon runners.

A consideration of the probable assets and liabilities of the body points to a shortage of glycogen being one of the most important factors in determining the limits of endurance in the Marathon.

The hearts of Marathon runners were found to be relatively larger than those of any other group of athletes examined. The significance of this finding and the possible fallacies in the X-ray measurement of heart size are discussed.

Five of the first seven places in the race were taken by men whom we had previously examined. There was no constant physical finding which would serve to differentiate these successful athletes from the less successful competitors.

The work has been done by both authors under the tenure of grants from the Medical Research Council.

We wish to express our thanks to Professor Buytendijk and his assistants for the trouble they took in providing us with such admirable facilities for making these observations at the Stadium, and to our colleagues Dr. Hoogerwerf of Leiden, Dr. Herxheimer of Berlin, and Dr. Best of Toronto, to whom we are indebted for the electrocardiographic, radiographic, and blood-sugar examinations respectively.

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DESCRIPTION OF PLATES.

PLATE 19, FIG. 2. Electrocardiogram of Case 994 who finished second in the Marathon. The *P–R* interval is 0·24 sec. The 'T' wave is of large amplitude in lead I and inverted in lead III. The displacement 'C' of the string in this and the succeeding electrocardiograms is due to the introduction of an E. M. F. of 1 m. v. for the purpose of checking the calibration.

FIG. 3. Electrocardiograms of a long distance runner showing right-sided ventricular preponderance with 'dropped beats' due to partial heart-block. The '*P–R* interval' in the cycles (×) following the ventricular lapses is of very short duration.

PLATE 20, FIG. 4. Electrocardiogram of a wrestler (Case 977) showing exceptionally large 'T' waves, and no iso-electric '*R–T* interval'. The 'T' waves start slightly before the 'R' waves return to the normal base line.

FIG. 5. Electrocardiogram from Case 550, a discus-thrower, showing a very high 'take off' of the 'T' waves.

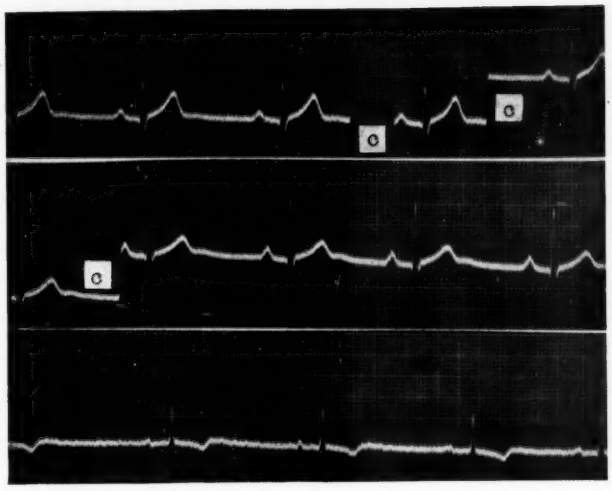

FIG. 2

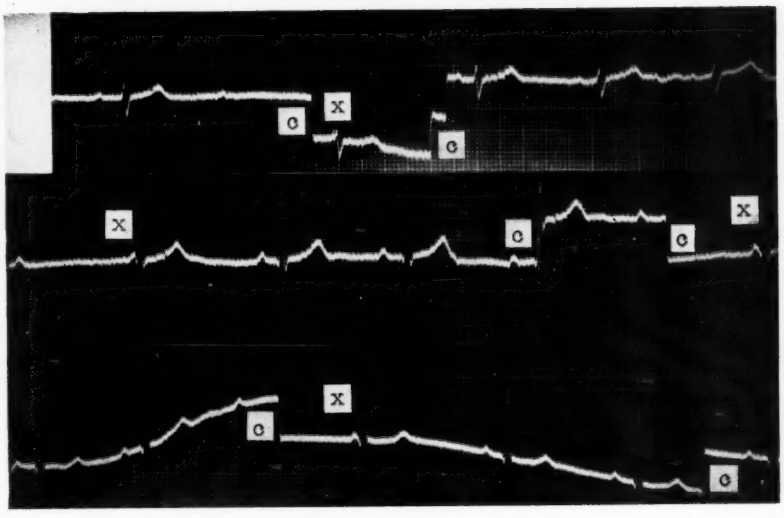

FIG. 3

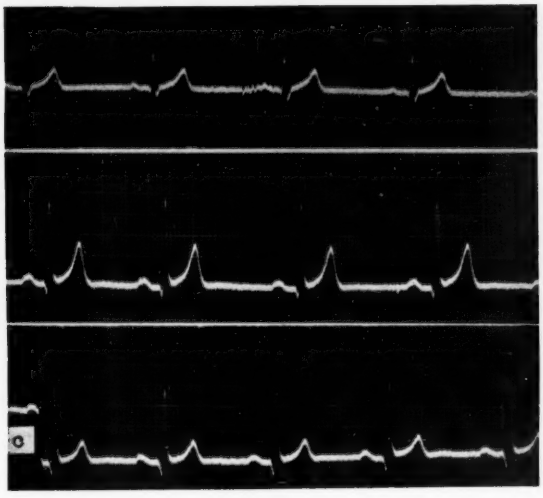

FIG. 4

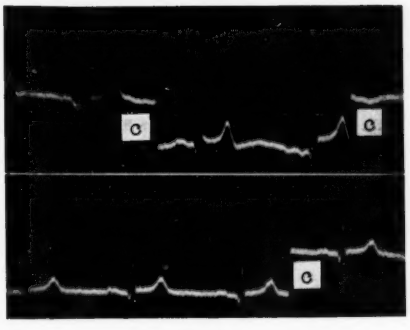

FIG. 5

616.514

URTICARIA

SOME OBSERVATIONS UPON THE VASCULAR REACTIONS IN THE SKIN [1]

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With Plate 21

In this paper it is proposed to examine some of the reactions of the skin in subjects suffering from spontaneous urticaria. It is necessary to define at the outset the meaning of certain terms, which have been applied to the cases and used repeatedly. The adjective '*spontaneous*' has been used for cases in which no specific factor, such as cold, light, or animals, could be found, so as to differentiate these from the '*specific*' types and also from cases of *urticaria factitia*, in which a hypersensitivity to stroking is present. These cases of spontaneous urticaria have been divided into three groups—transient, persistent, and giant. The term '*transient*' has been used to describe those cases of urticaria which usually start acutely and erupt quickly and in which the attack soon passes off; '*persistent*' has been employed for those in which the wheals continue to appear over a period of weeks or months; and the term '*giant*' has been applied to those which have very large and full wheals.

Lewis and his co-workers studied in great detail the vascular reactions of the skin to injury. They employed mechanical (stroke, scratch, pin-prick, &c.), thermal (heat, ice, &c.), and chemical stimuli (histamine, mustard gas, &c.) (9, 12, 13, 14, 15, 17, 18), and showed that a complex triple response follows all forms of injury, but that it may be modified to certain stimuli (such as ultra-violet light). This triple response consists of three independent reactions, namely, (*a*) a local dilatation of the arterioles, capillaries, and venules by direct action on the vessels; (*b*) a locally increased permeability of the walls of the minute blood-vessels by direct action, leading to local oedema of the skin, usually called 'whealing'; and (*c*) a widespread dilatation of the surrounding arterioles, known as the 'flare', and resulting from a local axon reflex. Lewis drew attention to the fact that many different forms of stimuli give rise to the same skin reaction and that this is a complex one. Search was made, therefore, for a common factor, and in his opinion this was tissue injury accompanied by the liberation of a substance which he called 'H-substance' from the skin cells and that this brought about the typical triple response. He has defined 'H-substance' as a 'liberated substance or substances having a histamine-like

[1] Received December 10, 1930.

action; i.e. any substance (or substances) that is liberated by the tissue cells and exerts on the minute vessels and nerve-endings an influence culminating in the typical triple response' (8). Lewis dealt only briefly with the application of this view to urticarias, in which the reactions of a triple response may be seen on the grand scale. He found that in urticaria factitia the patient exhibited only the reaction of a normal individual to a cutaneous injection of a given amount of histamine. There was no unusual sensitiveness to histamine. But as the reaction to a heavy mechanical stroke was exaggerated into the abnormal response of urticaria, he concluded that the unusual sensitiveness lay chiefly in the skin cells, which were easily irritated or damaged in such a way as to liberate an excessive amount of the H-substance, and that the quantity of this was responsible for the 'urticarial' effects on the vessels of the skin. Hare (4) carried out an experimental investigation of *specific* urticaria on the vascular reactions of the skin in patients susceptible to protein. He came to the conclusion that the skin reaction was due to the formation of an intermediate substance of a histamine-like nature and that the protein acts as the primary irritant.

The skin reactions of sixteen cases of *spontaneous* urticaria are here described, and a comparison is made with the response of normal skin to injury; further, the method of eruption of the wheals has been studied, and some observations upon transference of serum from subjects suffering from spontaneous urticaria are recorded and an attempt is made to show that the exciting factor of the attack, whatever its source and its nature, acts upon the skin cells and through them produces secondary effects upon the blood-vessels and so the urticarial phenomena.

Characteristics of the Eruption.

Before the wheal appears in a case of spontaneous urticaria, the skin becomes red, and usually the subject complains of local itching. The redness lasts for a varying length of time and then the wheal appears. The wheal may be red or white in colour, depending upon the rate at which the oedema is poured out into the tissues, and also upon the amount of fluid present in the wheal. Around the edge of the wheal a diffuse redness, having a more or less ill-defined margin, is present. We have, therefore, three definite parts in the urticarial reaction. There is a preliminary redness, which is often accompanied by the subjective sensation of itching; secondly, there is the wheal itself; and thirdly, around the wheal there is redness, which is not followed by whealing. Thus the urticarial reaction exactly simulates the typical triple response of normal skin to histamine; in certain other phenomena, of which the following are examples, this similarity is also seen.

It is sometimes possible to recognize that an urticarial patch is hotter to the touch than normal skin near to it; this is easier in the case of large than of small wheals. Precautions must, of course, be taken that both areas of skin

have been similarly exposed, and that the patient has not rubbed the urticarial patch. Accurate skin temperatures have been obtained by using a simple thermo-electric couple connected to a mirror galvanometer; this method has been found to yield satisfactory results and has been fully described by Lewis and Wolf (11). Five cases of urticaria were examined by this method; all showed an increase of temperature on the whealed skin. The differences ranged between 1·0° and 3·5° C., the average being 1·7° C. The results are fully shown in Table I.

I have been unable to trace any recorded observations on actual temperature readings in cases of urticaria, except those of Hallopeau (3) and of Dunlap and Lemon (2). Hallopeau, in 1902, noted a rise of temperature of 1° to 1½° C. (above the surrounding area) of the skin over a wheal in dermatographism, and thought that probably the same occurred in spontaneous urticaria, but he knew of no observations upon this point. Dunlap and Lemon, in 1929, stated that the temperature of an urticarial patch was 98·4° F. and that of a control area 94° F. in one of their cases, but they did not state how the temperatures were obtained.

The Congestion Test described by Lewis (8) has been used in five cases of spontaneous urticaria, four suffering from giant (Cases I, II, III, and IV), and one from persistent urticaria (Case VI). This test is employed to demonstrate an increased blood-flow in the skin, such as occurs when the arterioles dilate. A congesting pressure (70 mm. Hg. for three minutes) is imposed on the veins of a limb by means of a pneumatic cuff connected to a sphygmomanometer; skin with an increased blood-flow appears red in contrast to that surrounding it, which is cyanotic. In all of these five cases the urticarial patches appeared bright red on a purple background.

In one subject suffering from giant urticaria (Case II) affecting the left wrist, the eruption consisted of large wheals that spread extremely slowly up the limb. The man was examined lying down and having both arms on a level with the base of the heart. The veins proximal to the wheals (i.e. containing blood flowing away from them) were much more distended than those distal to them; those on the opposite limb were collapsed (see Fig. 1). The greater fullness of the veins, draining blood from the wheals, showed that in this one subject the blood-flow away from the wheal must have been considerably greater than from normal skin; since the blood-flow away from the wheals was increased, the blood-flow to them and in them must also have been greater than normal. This is consistent, therefore, with the findings about the temperature of the wheals and the results of the congestion test.

Refractoriness. Lewis (10) investigated a peculiar irresponsive condition of blood-vessels which he termed 'refractoriness'. When skin was damaged by various forms of injury (such as histamine puncture, stroking, freezing, &c.), and had become red and oedematous as a result of this stimulus, it was found at the stage when the oedema had subsided, but redness still persisted, that the tissue was refractory, absolutely or relatively, to a repetition of the same or any stimulus that produced a similar original lesion on control skin. This refractoriness

was a limited one, concerning only increased permeability, and depended upon a condition of the blood-vessels and not of the skin cells themselves. Lewis and Zotterman (16) found that this peculiar condition of blood-vessels known as refractoriness was present in their case of annular oedema.

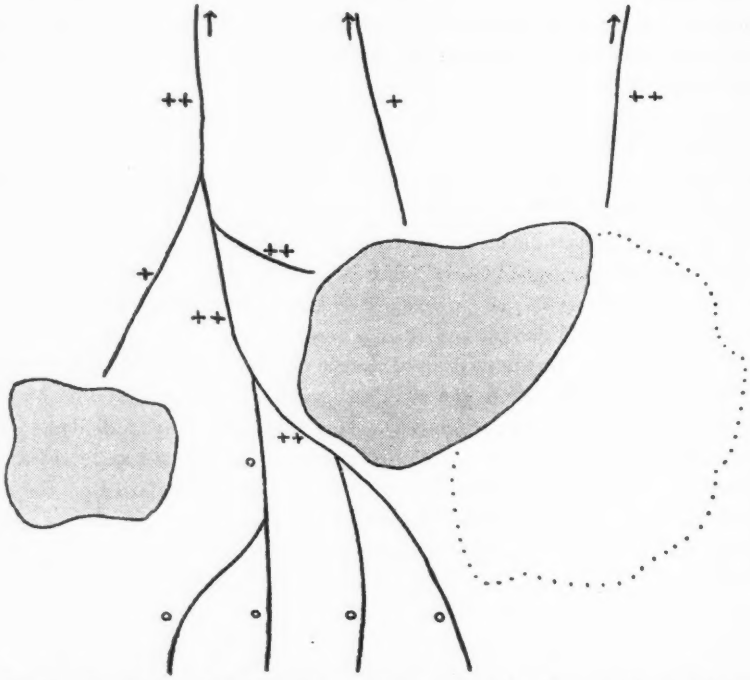

FIG. 1. *Case II.* Tracing from the forearm to show the enlarged veins leading away from two large urticarial wheals. The patient was lying down in bed and the arm was kept at the level of his heart, so that the effects were not due to increased venous pressure; moreover, the veins on the opposite forearm in similar circumstances were collapsed.
++ = greatly distended veins.
+ = full veins.
0 = collapsed veins.
Shaded areas = wheals up at time of observation (11 a.m.).
Dotted line = previously whealed area.

Certain reactions of previously whealed skin in cases of spontaneous urticaria have, therefore, been tested by various stimuli. The wheal was outlined in ink at the height of the reaction, and the effects of histamine on this area, after the wheal had completely subsided, were observed and compared with its effects on control skin. Similar observations were carried out, using a stroke stimulus. Finally, a large area of skin was observed in several cases, and all the wheals appearing on this were mapped out to see whether a previously whealed area would wheal again during the course of the day.

(i) *To histamine.* At different periods of time after the urticarial wheal had subsided, histamine was pricked into the skin and the size of the resulting wheal compared with controls on normal skin. If the skin that had been

recently whealed was still red, precautions were taken so that the histamine was not washed away as a result of the increased blood-flow in the red patch of skin; to do this, the circulation to the part was occluded for one minute immediately after puncturing in the histamine.[2] The strengths of histamine base used for testing refractoriness were 1 in 30,000 and 1 in 3,000, and on a few occasions 1 in 300. Nine cases were so tested on thirty-seven occasions; the results are shown in Tables IIA and IIB. In these tables, refractoriness has been divided into partial and complete; in partial refractoriness reduced wheals, and in complete refractoriness no trace of whealing, appeared on previously whealed skin, comparison being made with the controls. Previously whealed skin was found to be completely refractory to 1 in 30,000 histamine during the first few hours after the original urticarial wheal had subsided; on the next day refractoriness was no longer present. Occasional slight exceptions to this generalization were found. The full results after employing 1 in 30,000 histamine are given in Table IIA. With the more concentrated histamine (1 in 3,000 and 1 in 300), partial refractoriness was present immediately after the wheal had gone down, and this had disappeared on the next day. The results after 1 in 3,000 histamine are shown in Table IIB. It was found, moreover, that the degree of refractoriness had a definite relation to the fullness of the original urticarial wheal. Several subjects were tested, in whom wheals of different heights or degrees of fullness were present during the urticarial eruption; it was the rule to find that the higher and fuller the original wheal the more complete was the refractoriness of the blood-vessels in that area.

(ii) *To stroke.* All the cases of urticaria here recorded were capable of reacting to a heavy stroke stimulus by whealing; in other words, urticaria factitia was present in every case during the eruption of the rash. This is discussed in detail later. Refractoriness to stroke was tested by putting down the stimulus so that the stroke crossed the previously whealed area; a comparison could thus be made with the stroke response of normal skin on each side of the area being tested. Six subjects were so tested on eleven occasions. The results are given in Table III, and a typical result is illustrated in Fig. 2. This photograph was taken 4½ hours after the urticarial wheal had subsided. Each forearm was firmly stroked by means of a blunt-pointed instrument for three inches upwards from the wrist. The photograph shows that whealing occurred only on the proximal part and not on skin previously whealed; the control stroke on the opposite wrist resulted in uniform whealing. Refractoriness to stroke stimulus was, therefore, a phenomenon of previously whealed skin, and this passed off in twenty-four hours; this result resembled the reaction to histamine.

(iii) *To further spontaneous whealing.* Some subjects stated that they had

[2] The method of introducing substances into the skin has been that employed by Lewis (12), namely, pricking the skin lightly with a sharp needle through a drop of the fluid (e.g. histamine), but not drawing blood; the tests have, as a general rule, been carried out in triplicate and with controls, thus avoiding any possibility of a single anomalous result.

noticed that a patch of skin, which had been whealed in the morning, did not wheal again on the same day; such a history was given by Case IX and by Case XIV. The latter stated that after running one morning he sweated profusely and had been covered by an extensive urticarial eruption and had found that later in the day no urticaria followed a game of squash rackets, although this form of exercise usually brought out the rash. He was tested as follows: At 9.30 a.m. his skin was made to sweat by means of a hot-air bath and a subcutaneous injection of gr. 1/8th pilocarpine nitrate. All wheals on his arms resulting from this were outlined in ink. At 5.30 p.m. on the same day, all the wheals of the morning having subsided, he played squash rackets, and although many fresh wheals appeared on his arms no previously affected area whealed again.

In six subjects the eruption of the wheals was watched and each wheal mapped out in ink. In five of these (Cases II, IV, VII, IX, and X) no area once affected whealed again on the same day; on some occasions a wheal coming up during the afternoon was found to be indented by a previously whealed area, so that instead of appearing as a circular wheal it appeared as one with a notch in it. Such wheals were seen in three subjects (Cases IV, IX, and X). The one exception was a boy suffering from transient urticaria (Case VIII); his rash was characterized by rather low wheals that came up rapidly and lasted for a very short time. When observing his back on one occasion a wheal appeared and was outlined in ink; fifty minutes after its subsidence a fresh wheal appeared near to, and soon spread over, the whole area originally outlined.

Relation of Urticaria Factitia to Spontaneous Urticaria.

It has been shown by Lewis and his collaborators (1, 12, 14) that when normal skin is stimulated by linear stroking it reacts in one of three ways, varying according to the degree of pressure and also with the subject. When light pressure is applied to the skin, such as drawing the end of a flat ruler across it, a line of pallor, accurately marking out the area stimulated, develops. With firmer pressure a red line results; this is a uniform red flush, exactly following the line of pressure, and occurs on skin, to which the nerves have been cut, as well as on normal skin. In a number of subjects in whom the skin is hypersensitive, this red line is surrounded by an irregular area of bright red erythema. In other subjects, who are hypersensitive to mechanical stimulation, local oedema may follow the local red reaction, the condition then being known as dermatographism or urticaria factitia. Lewis and Grant (12) have examined the underlying cause of this condition. They have shown that the vascular reactions of the skin in urticaria factitia are identical with those following the intradermal puncture of histamine, and they concluded that the condition resulted from the liberation in the skin of a chemical substance

having a histamine-like action. These results were further elaborated by Lewis and Harmer (14).

Of the sixteen subjects in this series of spontaneous urticaria, who were investigated as regards the phenomenon of urticaria factitia, six were examples of transient, six of persistent, and the remaining four of giant urticaria. Care was taken to stroke skin that had definitely not been affected during the previous twenty-four hours and so made refractory. All the five subjects suffering from transient urticaria (Cases VII, IX, X, XII, XIII, and XVI) showed low but definite whealing in response to a heavy stroke; in one subject (Case IX) the onset of the reaction was delayed, the wheal not appearing for half an hour. Of the six persistent urticarias (Cases V, VI, VIII, XI, XIV, and XV) four showed good full whealing, and the other two gave low but quite definite wheals; the responses were all quite prompt. Of the giant types (Cases I, II, III, and IV) two gave full and two low whealing. In each of the subjects, who gave a full dermatographic wheal, the response took a considerable time to reach its maximal size; in Case I the wheal reached its full extent in three-quarters of an hour, but in Case III it continued to spread for twelve hours (see Fig. 3). Several urticarias due to specific factors, such as cold, light or cat, were tested, but none gave a dermatographic wheal on stroking the skin, since in these cases the skin reaction was specific to one form of stimulus only.

It is thus established that urticaria factitia can be excited during the eruption of spontaneous urticaria. Five subjects (Cases VII, VIII, IX, X, and XIII) were tested after its subsidence as well as during the eruption. In three subjects (Cases IX, X, and XIII), urticaria factitia could be excited during the acute attack but not after the attack had subsided. The fourth subject (Case VII) was even more interesting; he had an acute attack of spontaneous urticaria with definite urticaria factitia. After this attack had subsided, no whealing followed heavy stroking. On the next day, however, the urticarial eruption broke out again and was accompanied by urticaria factitia; both persisted until his death a few days later. The fifth subject (Case VIII) was an example of persistent urticaria; when first seen he had spontaneous urticaria and gave a full dermatographic wheal. The attack subsided and the urticaria factitia also disappeared. Two weeks later he had a fresh outbreak of spontaneous urticaria and the dermatographism returned with it. The further course of this case could not be traced, since the patient failed to report for further investigation or treatment.

In four subjects the dermatographic wheal was found to spread outwards to an abnormal degree in certain circumstances. The best example was seen in a patient suffering from giant urticaria (Case III); this phenomenon occurred on each occasion when his arm was stroked. The whealing began after an interval of half an hour and then gradually spread outwards, attaining its maximal size in 11½ hours. The width of the stroke, put down on the skin by means of a blunt point, was 4 mm. At the end of 3½ hours, the average width

of the wheal, in response to this stimulus, was 15 mm.; at the end of 11½ hours it measured 28 mm. across, the maximal width being 36 mm. Tracings were taken during the course of the spread at 3½, 4½, 6½ and 11½ hours after stroking the skin. These are shown in Fig. 3; the area stroked is indicated by the dotted line and the maximal extent of the original flare resulting from the stroke is shown by the interrupted line. In a second subject (Case I), suffering

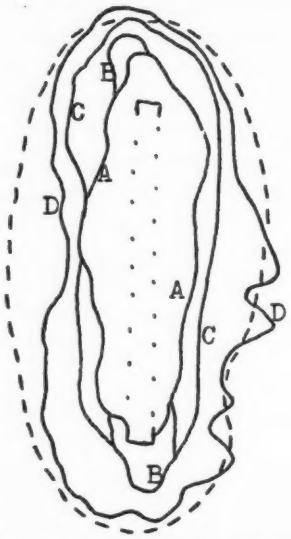

FIG. 3. *Case III.* Tracing to show extreme outward spread of dermatographic wheal. Firm stroke put down at 11 a.m.; the extent of the original stimulus is indicated by a dotted line, and of the original flare by an interrupted line.

A = wheal at 2.30 p.m.
B = wheal at 3.30 p.m.
C = wheal at 5.30 p.m.
D = wheal at 10.30 p.m.

At 10 a.m. next day this area was still red and slightly swollen.

also from giant urticaria, a widespread wheal occurred after stroking; this appeared quite promptly, being definitely palpable within four minutes of the stroking. It took three-quarters of an hour, however, to reach its full extent and then measured 10 mm. across, the maximal width being 12·5 mm.; the original stroke, as in all these tests for urticaria factitia, was 4 mm. broad. On the next day it was found that a haemorrhage had occurred into the deeper layers of the skin and into the subcutaneous tissue at the site of the dermatographic wheal. Case IV gave a low non-spreading dermatographic wheal under the usual conditions of testing; but if the veins of the limb were congested by means of a pressure of 70 mm. Hg., applied to the arm for twenty minutes after the stimulus was put down, the wheal spread outwards. When this method of congestion is employed in an otherwise normal subject exhibiting urticaria factitia, the dermatographic wheal will spread outwards for a little distance, but never for more than 1 or 2 mm. In this subject the wheal spread until it attained an average width of 11 mm., the maximum being 17 mm. The fourth

subject tested (Case VIII) usually gave no spread of his stroke wheal; on one occasion, however, the upper half of the stroke spread excessively. Under the effects of congestion at 60 mm. Hg. for twenty minutes, the wheal from stroking spread slightly more than the normal limits and attained an average width of 9 mm.

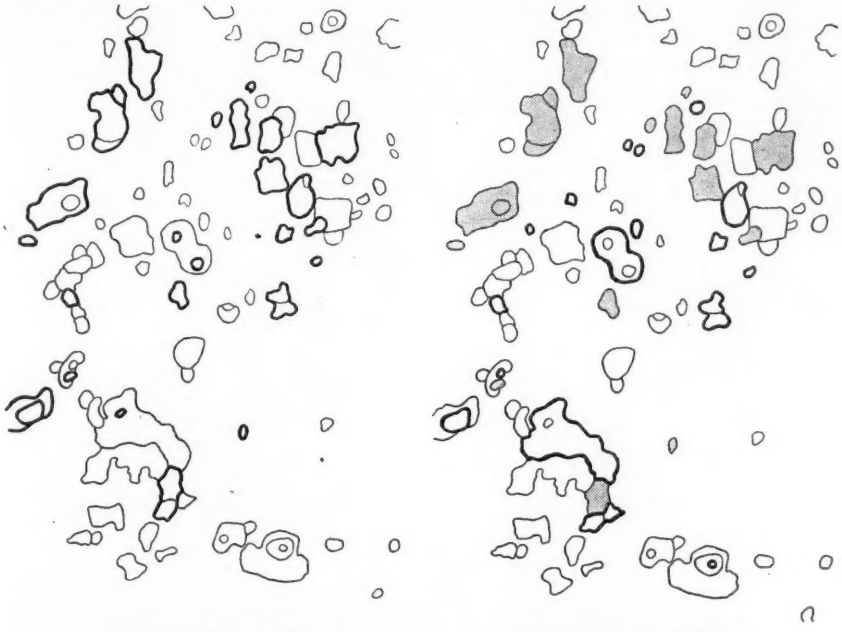

FIG. 4 (1). Rash at 11.5 a.m. FIG. 4 (2). Rash at 11.35 a.m.

FIG. 4. *Case IX.* A series of 8 tracings taken from a case of transient urticaria following anti-dysenteric serum therapy, to show the course of the eruption and spread of the wheals. In each figure pencil shading indicates skin, on which a wheal has previously formed and subsided completely; the heavy ink lines indicate areas of skin actually whealed at the time of observation. Light grey lines have been used to show all areas of skin affected during the whole series of observations.

Spread of Spontaneous Urticaria.

(a) *Eruption of wheals.* To arrive at any definite conclusions about the spread of the urticarial wheal it is necessary to study in detail a large number of wheals; for this, a suitable area of skin is marked out and every wheal appearing within this is recorded. A note is taken particularly of the time of its appearance and of its subsidence, and the extent of the wheal at various times is mapped out in ink. By transferring the ink lines to tracing paper an accurate pictorial record of the course of the eruption can be obtained; the average duration of a wheal in a patient can then be calculated. This method has been used for four subjects, two suffering from transient urticaria (Cases IX and X) and two from giant urticaria (Cases II and IV). The eruption in two cases is illustrated by a series of photographs taken from actual tracings of the rash (Figs. 4 and 5).

FIG. 4 (3). Rash at 12.5 p.m.

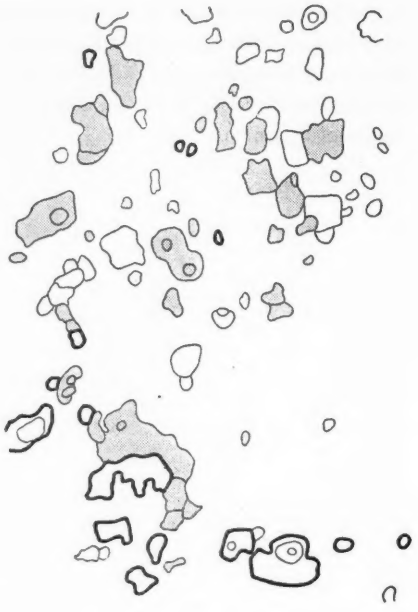

FIG. 4 (4). Rash at 12.35 p.m.

FIG. 4 (5). Rash at 1.30 p.m.

FIG. 4 (6). Rash at 2 p.m.

A short explanation of the method of reproducing these tracings is necessary. Every wheal appearing during the entire period of observation has been outlined by means of a faint grey line. In each figure thick black lines are also seen; these represent areas of skin actually whealed at the time that the observation was made. When a wheal has subsided, this area is covered in by pencil shading. Thus, in any one diagram, three areas of skin may be represented; faint grey lines mark out areas of skin that have not yet whealed but will subsequently do so; thick black lines show all wheals present at the time of observation; and shaded areas represent skin on which a wheal has appeared and completely subsided.

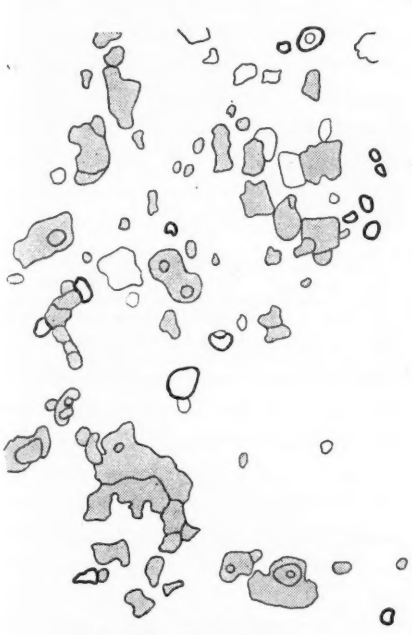

FIG. 4 (7). Rash at 3 p.m.

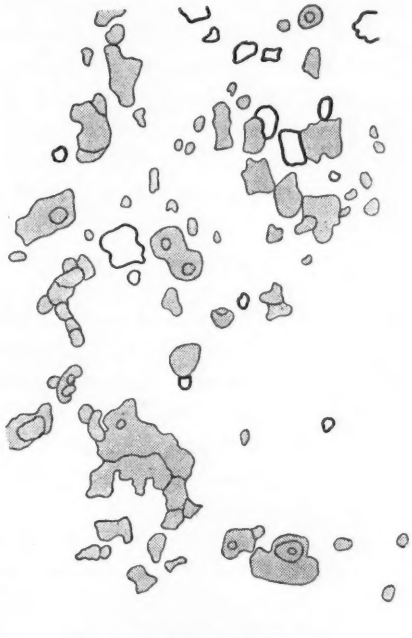

FIG. 4 (8). Rash at 3.45 p.m.

Figures 4 (1) to 4 (8) are a series of tracings from a patient (Case IX) suffering from transient urticaria occurring six days after receiving anti-dysenteric serum. Figures 5 (1) to 5 (4) come from a subject with giant urticaria, characterized by extremely slow spread (Case II).

Some further explanation of each series of maps must now be given. In Case IX, the rash was recorded at half-hourly intervals from 11.5 a.m. to 12.35 p.m., and then four times during the next three hours (Figs. 4 (1 to 8)). This subject's rash was characterized by wheals that rapidly attained their full size and lasted for a short time, the average duration being three-quarters of an hour; the majority did not tend to spread. A few wheals, however, spread outwards from a small centre. In one place (near the centre of the observed area) two small wheals, about 1 cm. apart, subsequently fused, forming an

8-shaped wheal. The phenomenon of refractoriness was quite well shown in this subject by the notching of a wheal that appeared at 1.30 p.m. (Fig. 4 (5)). An interesting example of a very slowly spreading series of wheals was seen in Case II. Records taken on two occasions on one day and twice on the next

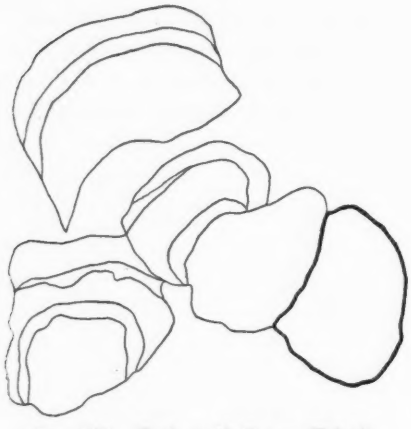

FIG. 5 (1). Rash at 10.15 a.m. (Feb. 6).

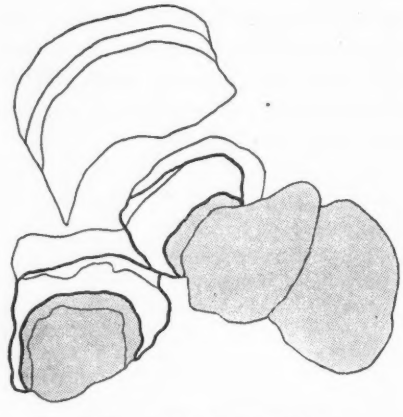

FIG. 5 (2). Rash at 3 p.m. (Feb. 6).

FIG. 5. *Case II.* A series of 4 tracings taken from a case of giant urticaria, spreading extremely slowly up the forearm from the wrist, to show the course of the eruption and spread of the wheals. In each figure pencil shading indicates skin, on which a wheal has previously formed and subsided completely; the heavy ink lines indicate areas of skin actually whealed at the time of observation. Light grey lines have been used to show all areas of skin affected during the whole series of observations.

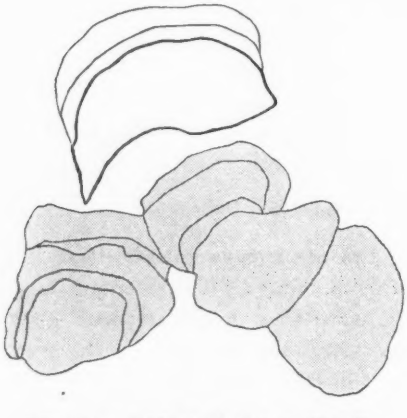

FIG. 5 (3). Rash at 10.30 a.m. (Feb. 7).

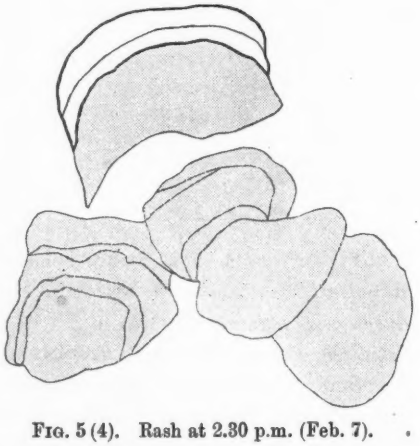

FIG. 5 (4). Rash at 2.30 p.m. (Feb. 7).

day are shown (Figs. 5 (1 to 4)). The situation of this rash was the flexor surface of the forearm just above the wrist. Presumably the area between the eruption at 3 p.m. on February 6 and 10.30 a.m. on February 7 was affected during the night; if this were so, then the diagram would be an uninterrupted one. This patient, an intelligent man and an artist by profession, left the

hospital on the afternoon of the 7th, but he wrote to me stating that he had watched the rash slowly extend up to the elbow during the next two days and that it had then stopped.

We can divide cases of urticaria roughly into two large groups according to their method of spread. There is a group in which the wheals reach their full height quickly; they are often quite small at first, but they spread rapidly and last for only a short time. In the other group, the wheals take a long time to attain their full size and are large; they extend slowly and they last for a relatively long time. There are, of course, intermediate types of eruption. The transient urticarias tend to fall into the former and the persistent and giant cases into the latter group. It would appear that the group of urticarias characterized by slow spread and long duration have a skin reaction, which is due to the slow liberation of H-substance, presumably in response to a slowly acting poison or internal agent. On the other hand, the more transient urticarias with a quickly-appearing, short-lasting wheal resemble much more closely the typical triple response of normal skin to injury and are probably due to the rapid liberation of H-substance, resulting from a quickly acting poison.

Several of the patients in this series gave a history that the urticaria was worse after a bath, in an evening, or when they were warm in bed, or at a dance, or in a cinema theatre. Such a history is not uncommon according to current text-books on urticaria. To test the effect of a hot bath, the left forearm and hand of one subject (Case IV) were immersed at 43° C. for ten minutes.[3] Within half an hour of removing the limb from the bath, about seventy wheals had appeared; no whealing occurred on the right forearm during the same period of time. This test was repeated on another day, and on this occasion about a dozen fresh wheals appeared. This reaction to hot water was not a specific one to heat, since the application of a metal box heated to various temperatures gave no whealing, such as can be produced by cold in cases of urticaria from cold. Five other patients were similarly tested, by immersion of a limb in a hot bath, but no increased whealing resulted in any of these subjects (Cases I, V, VIII, XII, and XIII).

(b) *Duration of the wheals.* Three patients in this series stated that they had noticed that each wheal lasted for a certain length of time. One (Case I) had found that the wheals lasted three to four hours; another (Case III) stated that the larger wheals lasted for about twelve hours and the smaller ones for three to four hours; and the third (Case V) gave five to six hours as the average duration.

For acquiring definite knowledge about the duration of a wheal, accurate observations must be made frequently and at short intervals. Five subjects have been observed; the results are recorded in Table IV. The average duration of the wheal in this series was 2¼ hours; a quarter of an hour was the minimal and six hours the maximal duration. The wheal in the transient

[3] This temperature is the hottest than can be endured without discomfort for this length of time.

urticarias tended to last for a shorter time than in the giant form. This supports the theory already discussed that the transient urticarial wheal has a close relation to the acute injury wheal, whereas the giant urticarial wheal is due to a more slowly acting injurious agent.

Presence of a Poison in the Blood.

Prausnitz and Küstner (19) in 1921 studied a case suffering from hypersensitivity to fish protein. Having failed to produce passive anaphylactic phenomena in guinea-pigs, they tried passive transference to normal men; on introducing the subject's serum intradermally into controls and testing the same area with fish extract twenty-four hours later, they were able to produce whealing, showing that passive transference could be carried out. Harris, Lewis and Vaughan (5) tested cases of specific cold urticaria and demonstrated the presence of a dermolysin in the blood in two out of three subjects; this acted on the skin cells in much the same way as the haemolysin on the red blood corpuscles in paroxysmal haemoglobinuria. Hof (6) in 1930 found an active substance in the blood of patients showing urticaria factitia; on injection of this into normal skin a wheal was produced, but in his opinion this was not due to histamine alone. Holzapfel (7) found on transfer of serum from patients with urticaria that the wheals were much larger when the serum was obtained after stroking the patient than before doing so.

As a result of the observations upon cold urticarias it was decided to test some cases of non-specific urticaria in a similar manner. Blood was obtained from the subject during an attack and the serum separated by means of a centrifuge. A small quantity (0·1 c.c.) of the patient's serum was then injected intradermally into a normal subject; a control was made at the same time and in the same way, using serum similarly prepared from a healthy adult with no history of urticaria. Such an injection results in a wheal with a surrounding flare. The two wheals from the control and urticarial serum are observed for half an hour, or longer if necessary, and a comparison is made between the two wheals and flares. Six subjects were tested by this method, four being cases of giant and two of persistent urticaria. The reactions in the transference test from one (Case IV) are here described in some detail as an example. Half an hour after the intradermal injection, the reaction from the patient's serum was at its height. A small low wheal resulting from the infection was still present at the site where the control serum had been introduced; however, no surrounding flare was present. A fair-sized wheal and bright surrounding flare marked out the site where the patient's serum had been introduced. Five different normal subjects were injected with the two sera; all gave the same differences in response. A photograph of the forearm of one subject is reproduced in Fig. 6. The wheals and the flares lasted in each of the five subjects for 2 to 2½ hours. The whealing from the control serum was in every case much less extensive than that of the patient's serum at all

stages after injection, except at the actual time of the injection, when both intradermal wheals were equal in size. On injecting his own serum and that of a control into the arm of the patient, no increased whealing and flare from his own serum resulted.

A second patient (Case II) gave a positive result to the transference test in a similar way; the response was increased whealing and a flare for the urticarial serum, compared with the control. A patient (Case I), with giant urticaria, which was accompanied by subcutaneous swelling under the urticarial wheals, also gave a positive reaction; the whealing was only slightly greater than the control, but subcutaneous swelling was definitely present and these areas were tender; three out of four normal subjects, into whom this urticarial serum was injected, gave this reaction, but the fourth showed no difference. Negative transference tests were given by the serum from three other patients (Cases III, V, and VI).

Discussion. In the tests described above it has been shown that although neither of the two persistent urticarial cases so tested gave a positive reaction, three out of four giant urticarias gave increased whealing and surrounding flares when compared with control injections. If we suppose that a person suffering from urticaria has a toxic body circulating in the blood, then it is reasonable to suggest that this body is the factor responsible for the liberation of H-substance in the skin, since it has already been proved that this is the underlying mechanism of the urticarial skin reaction. To account for the occurrence of wheals at one time and not at another, either a general condition resulting in a temporary increase of toxic body in the circulating blood, or some local change resulting in the sufficient release of H-substance itself locally, would be necessary. If we suppose that the toxic body in the blood is always liberating a small quantity of H-substance from the skin cells, insufficient itself to cause whealing, then any slight local injury of the skin, also insufficient by itself to produce whealing, may be enough to cause a wheal by the summation of the two effects. In favour of this suggestion are certain features, which must now be mentioned briefly.

The slow outward spread of urticaria factitia, as already noted, in some cases of spontaneous urticaria could be explained by the increased quantity of toxic body brought to the area immediately around the stroke wheal, as a result of the increased blood-flow in the flare. On the other hand, it is possible that the stretching of the tissues produced by the dermatographic wheal, which is usually full and high, damages the cells in the immediate neighbourhood and liberates a small amount of H-substance; this quantity, insufficient in itself to produce further whealing around and thus outward spread of an ordinary dermatographic wheal, succeeds in doing so in cases of urticaria by reason of the toxic body circulating in the blood, which itself is causing the liberation of small amounts of H-substance. A similar explanation could be given for the appearance of spontaneous whealing in the flares around histamine wheals, a phenomenon seen in one subject (Case IV). The

long-lasting reactions in many giant urticarias, especially conspicuous in Case II, presumably resulting from a slow liberation of H-substance, could be accounted for by the presence of a toxic body circulating in the blood. The increased whealing resulting from the hot bath in Case IV is also capable of explanation. The hot water damages the skin, producing the long-lasting red flush of the immersed skin (i.e. the first stage of tissue injury response) but no whealing; in this urticarial subject (and this patient gave a positive transference test) H-substance liberated by the toxic body in the blood, together with that freed as a result of the hot bath, results in whealing.

Attention has been drawn above, on more than one occasion, to differences between the persistent and giant forms of urticaria. It is now suggested that the main difference lies in the amount and type of toxic body in the blood; that the giant cases have a much more potent type than the persistent cases, and that, therefore, much more H-substance is liberated in the skin, resulting in fuller whealing. Support is given to this hypothesis by the positive transference tests in only the giant cases.

To summarize, it has been shown that the eruption in spontaneous urticarias resembles the triple response of skin to injury, which is due, according to Lewis, to the release of histamine or H-substance from the skin cells. Transference tests have yielded results that suggest that a toxic body is circulating in the blood and that whatever its nature and origin it acts by producing a definite skin reaction, known as spontaneous urticaria.

Summary.

1. The skin reactions in certain cases of spontaneous urticaria have been investigated. From the characteristics of the eruption, the increased blood-flow and the phenomenon of refractoriness, it is concluded that the mechanism is the same as for those urticarias which are specific to one type of stimulus (such as cold, light, and cat), i.e. the liberation of H-substance from the skin cells.

2. The spread of the urticarial wheal and method of eruption are discussed and illustrated by a series of diagrams. Some observations upon the duration of the wheals are recorded.

3. Some additional observations upon the relation of urticaria factitia to spontaneous urticaria are noted. All the subjects suffering from spontaneous urticaria gave urticaria factitia on stroking; this phenomenon passed off as the attack of spontaneous urticaria subsided. In a few subjects the dermatographic wheal spread slowly outwards involving a wide area of skin.

4. The results of some transference tests with serum from subjects of spontaneous urticaria are recorded, and the evidence for the presence of a toxic body in the blood of these subjects is briefly discussed.

I am indebted to the physicians of University College Hospital for permission to investigate their patients, and more especially to Sir Thomas Lewis for much valuable help and criticism in carrying out the observations.

This work has been undertaken on behalf of the Medical Research Council.

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TABLE I

Temperature of Wheals and of Normal Skin in Cases of Urticaria.

Case.	Type.	Site.	Room temperature.	No. of readings each.	Control.	Urticarial.	Difference.
I.	Giant	Arm	16° C.	9	28·2° C.	31·7° C.	3·50° C.
III.	,,	,,	18°	7	29·6°	30·65°	1·05°
IV.	,,	Wrist	17°	6	30·75°	32·6°	1·85°
V.	Persistent	Back	17°	5	30·6°	31·6°	1·00°
VI.	,,	Chest	19°	4	29·05°	30·2°	1·15°

TABLE II A.

Effects of 1 in 30,000 Histamine on Skin previously Whealed.

Case.	Type.	Site.	Hours after subsidence.	Refractoriness.
I.	Giant	Wrist	½	+
IV.	,,	Forearm	1	+
IX.	Transient	,,	1	+
I.	Giant	Wrist	1½	P
I.	,,	,,	2¼	+
I.	,,	Arm	2½	P
IV.	,,	,,	5½	+
V.	Persistent	Back	*c.* 12	+
IX.	Transient	Wrist	20	0
I.	Giant	,,	24	0
III.	,,	Chest	24	0
III.	,,	Abdomen	24	0
II.	,,	Wrist	24	+

N.B. + = fully refractory (no trace of whealing).
P = partially refractory (reduced whealing).
0 = not refractory (normal whealing).

TABLE II B.

Effects of 1 in 3,000 Histamine on Skin previously Whealed.

Case.	Type.	Site.	Hours after subsidence.	Refractoriness.
III.	Giant	Back	¼	P
VIII.	Persistent	Arm	½	P
IX.	Transient	Forearm	¾	+
IV.	Giant	,,	1	P
IV.	,,	Back of knee	1	P
VIII.	Persistent	Back	1	P
VIII.	,,	,,	2	P
VIII.	,,	,,	2	P
IX.	Transient	Forearm	2	+
I.	Giant	Wrist	2½	P
I.	,,	Arm	2½	0
X.	Transient	Forearm	3	+
X.	,,	,,	3	P
VII.	,,	,,	*c.* 4	P
IV.	Giant	Arm	5½	P
V.	Persistent	Back	*c.* 12	P
II.	Giant	Wrist	24	P
IV.	,,	Back	24	0
I.	,,	Wrist	24	0
IX.	Transient	Forearm	24	0

N.B. Abbreviations as for Table II A.

TABLE III.

Effects of Stroke on Skin previously Whealed.

Case.	Type.	Site.	Hours after subsidence.	Refractoriness.
I.	Giant	Wrist	Subsiding	+*
I.	,,	,,	$\frac{1}{2}$	+
IV.	,,	Arm	$\frac{1}{2}$	+
VIII.	Persistent	Back	$\frac{1}{2}$	P
VIII.	,,	,,	1	P
I.	Giant	Wrist	$1\frac{1}{2}$	+
I.	,,	,,	$2\frac{1}{2}$	+
XIV.	Persistent	Arm	5	+
IX.	Transient	Chest	5	+
XIV.	Persistent	Arm	$16\frac{1}{2}$	+
III.	Giant	Chest	24	0

N.B. Abbreviations as for Table II A.

* No further whealing occurred on skin which had still a faint trace of whealing when tested.

TABLE IV.

Duration of Urticarial Wheals.

Case.	Type.	Number of Observations.	Duration (in hours). Minimum and maximum.	Duration (in hours). Average.
IX.	Transient	23	$\frac{1}{4}$ to $1\frac{1}{4}$	$\frac{3}{4}$
X.	,,	14	$\frac{3}{4}$ to 3	1
I.	Giant	1	—	6
II.	,,	5	$\frac{3}{4}$ to $3\frac{1}{2}$	$2\frac{1}{4}$
IV.	,,	18	$\frac{3}{4}$ to $4\frac{1}{2}$	$1\frac{1}{4}$
Average	—	61	$\frac{1}{4}$ to 6	$2\frac{1}{4}$

Case Summaries.

Case I. M. D., a single woman, aged 30, complained of nettle-rash, which had been present for three months. It started on her hands and forearms, appearing at any hour of the day, but especially at night, when warm in bed; she found that it also came up when she was nervous, but not on taking a hot bath. She could trace no relation of the attacks to any article of diet. The rash had affected all parts of the skin, including that of the fingers and toes; on one occasion her lip was swollen, and on another her tongue became so large as to interfere with swallowing. Each wheal lasted for three to four hours. She had had no previous attacks, and there was no family history of urticaria or asthma.

Past illness. Nothing of importance except (i) septic tonsils, removed two months before, and (ii) pyorrhoea, treated by extraction of twenty-two teeth one month before.

Accessory findings. Nothing abnormal in chest or abdomen. The blood Wassermann reaction was negative. The protein skin tests were all negative.

Rash. The wheals were large, red, and tense, with considerable swelling; subcutaneous swelling was often present too. The lesions were usually few in number. On one occasion the mucous membrane of the lip was severely affected.

Case II. A. T., a married man, aged 59, an artist; admitted under the care of Mr. E. A. Peters. On the appearance of urticaria six days after tonsillectomy and an operation for a deflected nasal septum, he gave the following history. He had had attacks of nettle-rash for twenty years; each attack had followed a chill, and the usual interval between each was one year. He had been unable to trace any relation to food, and knew of no exciting factor other than chill. The wheals usually appeared on the limbs and had affected the soles of the feet, and also the tongue. Attacks lasted from two to seven days. Had noticed that the wheals gradually spread; for example, wheals appearing on the fingers would extend to the hand and then up the forearm. Stated that it never came out again on an area, which had been previously affected, during the same attack. No family history of urticaria or asthma.

Past illness. Nothing, except frequent chills, and last year an attack of bronchitis and asthma.

Accessory findings. Nothing abnormal in chest or abdomen. The protein skin tests were all negative, except to shellfish and seasonings.

Rash. At first the tongue was swollen to about twice its normal size. On the right elbow and wrist were urticarial plaques. On the next day these had disappeared, and new lesions were seen on the left wrist and over the sacrum. The area on the left side spread slowly up the forearm. The wheals were large and full.

Case III. F. S., a married man, aged 33, a carman; complained of nettle-rash for the last twelve months, never having been free of it. It occurred mostly at night when in bed, but hot baths did not make it worse. Had observed that the larger plaques lasted for about twelve hours, the smaller ones only three to four hours. No relation to food had been traced.

Past illness. None.

Accessory findings. No abnormalities in chest or abdomen. Blood Wassermann reaction negative.

Rash. Large, and a few small, wheals, often quite high, appeared on all parts of the body; they were never very numerous.

Case IV. P. M., a married man, aged 61, complained of nettle-rash for one year; he had never been free of it for more than three days since its onset. The rash occurred mostly on the trunk and lower limbs, especially in the evening. He also noticed that it came up frequently on lines of pressure. He could trace no relation to food.

Past illness. None.

Accessory findings. Nothing abnormal in chest or abdomen. Blood Wassermann reaction negative.

Rash. Large numbers of wheals, usually quite large in size and full, appeared on all parts of the skin, especially on the back.

Case V. A. N., a single man, aged 20, a tailor; he attended the casualty medical department for nettle-rash of five months' duration. The rash started as small white spots, which gradually spread outwards to form white rings. Usually only two or three plaques appeared in a day, but he had found that they came out more at night and on getting hot, such as on sitting in front of a fire or dancing. Each spot lasted for five to six hours, excepting those spreading to form rings, which lasted for about one day. He had had one previous attack four years ago, lasting two weeks.

Past illness. None.

Accessory findings. Nothing abnormal in chest or abdomen. The blood Wassermann reaction was negative.

Rash. Small, low, white plaques were seen on the face and chest. Some were ring-like.

Case VI. L. H., a schoolboy, aged 13, had suffered from nettle-rash for seven years. His mother had noticed that it was worse when he was nervous or excited, and often in the evening; sometimes the wheals appeared after a hot bath. For the first few years he had attacks every six months, lasting only a few days; but now he is never free. No relation to food could be traced, except possibly to eggs and cheese.

Past illness. (i) Scarlet fever, followed by ? serum sickness, one year ago. (ii) Influenza, six months ago.

Accessory findings. Nothing abnormal in chest or abdomen. The blood Wassermann reaction was negative. The protein skin tests were all negative, except to eggs, milk, and cheese.

Rash. Small, low, red wheals were seen on the body and arms; the eruption was fairly profuse.

Case VII. W. E., a single man, aged 17, a gardener; admitted on account of recurrent subacute rheumatic fever. Urticaria appeared two days after tonsillectomy and he then gave the following history. He had frequently suffered from attacks of nettle-rash, especially when ill. He knew of no predisposing factor, except ill-health.

Accessory findings. The heart was slightly enlarged, and developed mitral stenosis was present.

Rash. Extensive urticaria was found on the legs and arms; this rapidly became confluent so that scarcely any unaffected skin could be found on the next day. The wheals were low and red.

Case VIII. W. D., a schoolboy, aged 9, complained of nettle-rash for two days and had never had a previous attack. No other member of his family suffered from urticaria.

Rash. Numerous small, low urticarial patches were present on the chest; they appeared and faded quite quickly.

Case IX. K. H., a single woman, aged 42, admitted for bacillary dysentery and arthritis. She was treated by means of intravenous injections of anti-dysenteric serum. Six days after the first injection she developed urticaria; the attack lasted for only four days. She had never suffered from urticaria previously.

Rash. This started as a red flush and spots, which became urticarial within twenty-four hours; the wheals spread and faded rapidly, appearing on all parts of the skin; each wheal tended to be small, low, and red.

Case X. J. M., a single woman, aged 61, admitted for a rash affecting the toes. Whilst in hospital she developed an acute attack of urticaria, which lasted for four days; she attributed this to eating shrimps two days previously. She had never had a previous attack.

Accessory findings. Nothing abnormal in chest or abdomen. She had epidermophytosis of the toes. Blood Wassermann reaction negative.

Rash. Numerous large and small wheals were present on all parts of the skin, especially on the chest and extremities. The rash was characterized by its rapid spread with fusion of wheals arising near to one another.

Case XI. M. D., a house-physician, aged 24, who had suffered from urticaria since the age of 9. He had found that it usually came out after taking a hot bath; the wheals developed whilst he was drying himself and not during the bath. He knew of no relatives suffering from a similar condition except an uncle, who also had paroxysmal rhinorrhoea.

Case XII. M. B., a schoolgirl, aged 11, was brought up with a history of abdominal pains throughout the previous night; this was thought to have been due to eating chillies. The rash had appeared whilst at school during the morning; this lasted for only one day. She had had no previous attacks and there was no history of urticaria or asthma in the family.

Rash. Large and small, low, red wheals were present over the skin of the whole body; in many places they were confluent.

Case XIII. H. H., a medical student, aged 23, complained of generalized nettle-rash for three weeks. Had at first noticed irritating wheals on the thigh; since then they had appeared on the forearms and legs. Had found that the rash became worse if he stood before a fire. Had had no previous attacks and knew of no relative with urticaria or asthma. The rash consisted of small wheals on the arms, thighs, and legs. In addition there was evidence of scabies, localized to the perineum. When the scabies was cured, no further urticaria occurred.

Case XIV. G. W., a medical student, aged 24, had suffered from urticaria for ten years. Had found that it occurred most commonly on exercise or after hot baths, but that it also came out on excitement or in a hot room. He had observed on one occasion that a profuse eruption occurred on running, and that later in the day when he played squash rackets, a form of exercise that almost invariably produced urticaria, no new rash developed. There was no history of urticaria in any other member of the family. The rash, seen after exercise, consisted of a large number of wheals, combined with a diffuse erythema of the skin, on the trunk and limbs. The majority of the wheals were about 1 cm. across, but in a few places were confluent.

Case XV. F. C., a married woman, aged 64, had had nettle-rash for six months; she found that it usually came out in the evening, especially when sitting in a comfortable chair. The rash, which consisted of small red wheals, occurred mainly on the buttocks and lower extremities.

Case XVI. E. C., a single woman, aged 29, gave a history of indigestion of six months' duration; no ulcer was found. On examination several red wheals, varying from 1 to 3 cm. across, were found on her back. She then said that she had had urticaria for three weeks, following multiple midge-bites; the wheals had never been very large and usually only one or two occurred at a time.

FIG. 2. *Case I.* Photograph to show refractoriness of previously whealed skin to stroke stimulus. The ink line mapped out an area of skin just above the wrist, whealed by spontaneous urticaria 4½ hours before. A heavy stroke was put down and this whealed along its whole course, except on previously whealed skin. On the other wrist a stroke gave uniform whealing under similar conditions.

FIG. 6. Photograph of forearm from control subject to show result of a transference test. 0·1 c.c. of serum from Case IV has been injected into the skin on the left and 0·1 c.c. of serum from a normal subject into the skin on the right; both needle punctures can be clearly seen. The serum was injected ¾ hour before the photograph was taken. Note the bright flare and slight swelling around the urticarial patient's serum and the complete absence of any reaction around the control. *N.B.* The two T-shaped areas of reddening were from old ultra-violet light burning and should be ignored.

616.74–002.2

GENERALIZED MYOSITIS FIBROSA [1]

By J. A. G. BURTON, JOHN COWAN, and JOHN FLEMING
(From the Glasgow Royal Infirmary.)

In 1923 (This Journal, 1923–24, xvii, 103–10) we reported a case of generalized myositis fibrosa which had come under our observation in 1920. Since then we have seen the patient at frequent intervals, and now report upon her present condition (September, 1930) ten years after the onset.

She had been a healthy woman until the spring of 1920 when, pregnant for the fifth time, she noticed that her legs were somewhat stiff. In May she miscarried. In June the stiffness of her legs had increased to such a degree that she was unable to walk for any distance, and her arms were becoming stiff. Her difficulties increased, and in September, when admitted to hospital, she was very helpless, unable to turn in bed without assistance or to attend to herself in any way. The movements of the joints, which were normal, quite free within certain limits, were suddenly checked at definite angles from the shortness and tightness of the muscles. She was unable to touch her eyes with her fingers or to fully extend her arms. The movements of the fingers were ample but weak. She could not dorsiflex her ankles to a right angle, and flexion at the knee and hip was very limited. The lumbar spine seemed stiff.

A portion of the gastrocnemius was excised, and showed myositis.

Improvement followed, and in February 1923, she was very well and doing all her housework save that which required kneeling, e.g. scrubbing the floors.

Her subsequent health has been good, and she runs her household without difficulty, doing the washing and scrubbing the floors, &c.

She is well nourished and looks in good health. She makes no complaint, and walks well, even when viewed in bathing kit. There is still some limitation in the movements of the limbs. The shoulders are normal, but she cannot extend the left elbow as far as formerly, though the extension of the right elbow is greater. The right wrist cannot be fully extended, while the left has full movement. There is considerable disability in the hands. Flexion of the fingers is full but extension is limited, the maximum extension being shown in Figs. 1 and 2. The difficulty concerns the proximal interphalangeal joints, and the terminal phalangeal joint of the left index finger is enlarged and fixed in a semiflexed position from a chronic arthritis.

Flexion of the hips is less free than it was, but that of the knees is maximal. The ankles are mobile, but dorsiflexion does not reach a right angle. The movement of the toes is limited. The movements of the lumbar spine are

[1] Received January 13, 1931.

normal, but flexion of the cervical spine is limited, an old story she says, but we have no note of its previous existence. The expansion of the chest measures 6·5 cm. When rising from the prone position she still climbs up her legs in the same way as a child with pseudo-hypertrophic paralysis, so the extensor muscles must be weak though she is not inconvenienced.

The muscles generally are small and firm, but not sufficiently so to attract attention. The overlying skin is rather smooth and thin, but of fairly good texture. The ulceration has not recurred.

Her organs are healthy and the joints, save for the one exception, normal. The urine is sterile. The reflexes are normal.

She says that her difficulties vary from time to time, and are greatest in cold weather. Our observations confirm this, as her movements are less free in winter. We have, too, noticed at these times that the fingers were blue and the hands cold.

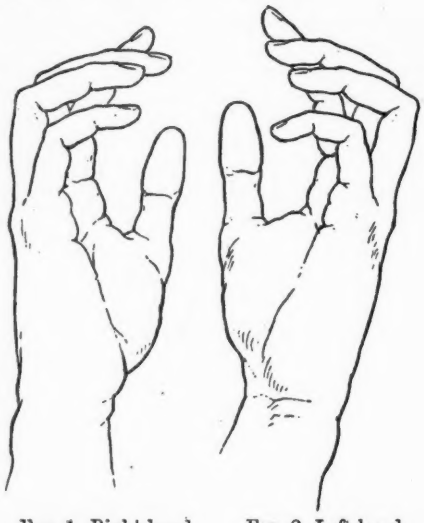

FIG. 1. Right hand. 15.ix.30.

FIG. 2. Left hand. 15.ix.30.

On the whole it is clear that her difficulties are increasing, but the progress is slow. She has, too, conquered her disabilities, and is able to perform all her duties with success, ten years after the onset of her illness.

Maximum.	1920.	1921.	1922.	1930.	
Right elbow, extension	99°	—	154°	170°	flexion full
Left elbow „	111°	—	150°	130°	
Right knee, flexion	102°	23°	17°	max.	extension full
Left knee „	89°	23°	7°	max.	
Right hip, flexion	126°	108°	68°	85°	extension full
Left hip „	126°	106°	48°	80°	

Figs. 1 and 2 show the present condition of the hands, with the fingers extended as far as is possible.

But one other case has been recorded since 1923 (1). The patient was a negro boy, aged 15, who died, apparently from tuberculosis, about fourteen months after the onset of his illness. The case is reported from the biochemical standpoint, and the clinical details are scanty.

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616.832.9—008.8

INORGANIC CONSTITUENTS OF CEREBROSPINAL FLUID[1]

I. CALCIUM AND MAGNESIUM

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Most of the inorganic constituents of blood-serum are present in approximately the same concentrations in cerebrospinal fluid, and also in pleural, peritoneal, ascitic, and oedematous effusions. Calcium, chloride, and magnesium are exceptions, but each in a different way. Thus of the total serum calcium only 50–60 per cent. is present in cerebrospinal and other body fluids, and this relationship is explained by the fact that the same percentage is found in ultrafiltrates and dialysates of serum. Chlorides, on the other hand, are found in *greater* concentrations in the cerebrospinal fluid than in serum. The whole of the serum chloride is dialysable, and other body fluids and ultrafiltrates usually contain a higher concentration than the serum itself. Magnesium also has been found in greater concentration in cerebrospinal fluid than in serum, but all the serum magnesium is *not* dialysable, and exudates contain only about 80 per cent. of the serum value and therefore considerably less than the cerebrospinal fluid. Magnesium, therefore, seems to be unique amongst the inorganic constituents of the body, and for this reason to be worthy of more detailed study than it has hitherto received. This paper forms a preliminary communication on the subject. Although calcium has been more carefully investigated, we have made a simultaneous study of this element for comparative purposes.

Historical.

Normal human serum contains in all 9–11 mg. of calcium per 100 c.c., while the cerebrospinal fluid is generally considered to contain about 5·0 mg. of calcium per 100 c.c. Variations from the latter are normally from about 4·4–6·6 mg. per 100 c.c. (1, 2, 3, 4), although Critchley and O'Flynn (5) give the average normal as high as 6·2 mg. per 100 c.c. Kral, Stary, and Winternitz (6) are the only observers who found the concentration in serum and cerebrospinal fluid nearly equal, and before their figures can be accepted their technique must be further investigated.

[1] Received November 24, 1930.

Most workers also agree on the *dialysable* fraction of serum calcium. The most extensive work has been carried out by Greenberg et al. (7, 8, 9), and they give the normal range of this fraction to be from 4·2–6·8 mg. per 100 c.c., with an average of 4·96 (7, 8). An analysis of their figures (omitting obviously abnormal results) in various papers (9, 7, 8) show the average dialysable fraction to be 50 per cent. of the total serum value. Greenberg himself considers this a misleading method of expressing the results, inasmuch as the diffusible calcium is more constant, even in the normal individual, than the total serum calcium (10). Cushny (11), using ox-serum, found 62–70 per cent. filtrable. Tschimber and Tschimber (12) found 50–60 per cent. of the serum calcium in ultrafiltrates, and Stary and Winternitz (13) 57 per cent. Results completely at variance with the above were obtained by Bernhard and Beaver (14) who applied the method of electrodialysis. In their experiments the calcium showed the widest variations, being in some cases completely dialysable and in others completely non-dialysable.

Comparatively little work has been done on magnesium. Practically the only serious study is that by Cohen (15, 16) who found an average cerebrospinal fluid value of 3·28 mg. per 100 c.c., compared with an average serum value of 2·56. The cerebrospinal fluid value was practically constant, and was independent of age, sex, cell, or protein content, or Wassermann reaction. Unfortunately for comparative purposes the serum magnesium of his cases also showed practically no variation. He tried to remedy this by injecting magnesium sulphate intramuscularly and did not succeed in altering the cerebrospinal fluid value. As, however, the percentage of magnesium in the serum quickly returned to normal in his cases, and as we do not know how long it takes for the serum-cerebrospinal equilibrium to be established, conclusions drawn by this method are open to criticism. We felt that to establish Cohen's conclusions that the percentage of magnesium in the cerebrospinal fluid remains constant in spite of a considerable rise in the percentage of magnesium in the serum, a larger number of cases were necessary, more especially cases showing natural variations in the concentration of serum magnesium.

The percentage of magnesium in oedema fluid, unlike that in cerebrospinal fluid, is always lower than that in the serum (17, 18). Stary and Winternitz (13) found about 82 per cent. of the total serum magnesium present in ultrafiltrates, and this figure, corrected for the space occupied by insoluble material according to the formula of Polanyi (19), gave the dialysable magnesium as 72 per cent. This agrees with the figure (70 per cent.) given by Tschimber and Tschimber (12).

A few figures only are available for mental diseases. Eisler (20) investigated a large number of cases of varieties of meningitis, and states that in infective meningitis the magnesium content of the cerebrospinal fluid is so constantly raised as to be of diagnostic value. In luetic diseases of the central nervous system various changes from the normal were found. The normal figures given by this worker, however, are undoubtedly wrong (1·0–1·2 mg. per 100 c.c.), and we feel that little reliance can be placed on the comparative

values. Weston and Howard (21) found no difference between serum and cerebrospinal fluid magnesium in manic-depressive insanity, either in the manic or depressive phase. Their figures are very low (average 2·4 mg. per 100 c.c.) and suggest that a faulty method of estimating the magnesium was used.

Methods.

Calcium. Collip and Clark's (22) modification of Kramer and Tisdall's (23) method.

Magnesium. The general technique was that described by Watchorn (24), but throughout the present work the Bell-Doisy (25) reagents have been used to develop the colour instead of Brigg's (26) reagents. The colour-tint of the unknown and standard have been found to be a better match with the former reagents. For the present type of work, where the greatest possible accuracy is required, it is essential that the standard and unknown should be of very nearly the same strength. Certainly the colorimeter readings should not differ by more than three whole divisions of the scale, and this precaution has been observed throughout.

Ultrafiltration. Greenberg and Gunther's method (27).[2]

Serum proteins. (*a*) Total protein. 0·25 c.c. serum was added to 5 c.c. normal saline and precipitated by the sodium tungstate-sulphuric acid technique in a centrifuge tube. After spinning down the precipitate, the supernatant liquid was poured off, the precipitate re-dissolved in sodium tungstate and saline, and reprecipitated by acid. After centrifuging the precipitate, solution and reprecipitation were repeated a second time. Finally the precipitate was washed into a standard modification of the Kjeldahl apparatus and the nitrogen determined.

(*b*) Albumin. 0·75 c.c. serum was added to 9·25 c.c. saturated $Mg.SO_4$ solution containing crystals of $Mg.SO_4$ and the precipitated globulin filtered off through a small paper. 5 c.c. of the crystal clear filtrate was then treated with the tungstate and acid exactly as described under total protein. Blank determinations were made of all the reagents, and the factor 6·25 used to convert the nitrogen to protein. The difference between the total protein and albumin was taken to represent globulin.

All determinations have been made in duplicate throughout this work when quantities of material allowed. Cerebrospinal fluid was always examined in duplicate, and about 60 per cent. of the sera. Agreement between duplicates has been such a satisfactory feature of our technique that we have no hesitation in including those determinations not so made.

All sera containing a trace of haemoglobin were entirely discarded.

[2] One of us (E. W.) is greatly indebted to the kindness and courtesy of Dr. Greenberg, who not only gave personal instruction but also the apparatus which had been made for his own use.

Source of Cases and Materials.

The cerebrospinal fluids were all obtained by lumbar puncture and the bloods by vein puncture with a minimal amount of stasis.

The cases were selected (1) from patients admitted to neurological and general wards of King's College Hospital; (2) from patients whose blood and cerebrospinal fluid were sent to the Maudsley Hospital from other London County Council Mental Hospitals for diagnostic purposes; (3) from patients in the Maudsley and other London County Council Mental Hospitals whose blood was taken specially for this examination.

After collection, or as soon as received, the cerebrospinal fluids were placed on ice after one drop of chloroform had been added. The serum was separated from the corpuscles as soon as practicable, generally within six, and always within eighteen, hours. The protein determinations were commenced at once and the remaining serum placed on ice. The same evening both serum and cerebrospinal fluid were transferred to small vaccine bottles and posted to Cambridge. Estimations were commenced the following morning, and if this were not practicable the specimens were again placed on ice. Samples were never posted on a Saturday.

Experimental Results.

The values obtained for magnesium in serum ranged from 2·00 to 4·05 mg. per 100 c.c. Table I shows the whole series of cases, grouped according to diseases. The cerebrospinal magnesium shows a mean of 3·33 mg. per 100 c.c. The lowest percentage was 2·83 and the highest 3·90, but these extremes were rarely found. Even including these abnormal values, the average deviation from the mean is only $\pm 0{\cdot}19$ mg. per 100 c.c. Our results absolutely confirm Cohen's conclusions that the magnesium of cerebrospinal fluid is independent of protein content and Wassermann reaction. Further, in no disease for which we have sufficient figures have we ever found the cerebrospinal fluid magnesium consistently changed in one direction or the other; in general paralysis for instance, figures varied from 2·99 (Case 92) to 3·78 (Case 96) mg. per 100 c.c. For these diseases in consequence, magnesium determinations appear to have no diagnostic value. Being satisfied, therefore, that neither the diagnosis, the Wassermann reaction, nor the presence of excess of protein consistently alters the cerebrospinal fluid magnesium in one direction or the other, we have arranged our results to show the relation between the values found in the serum and cerebrospinal fluid (Table II).[3]

[3] As our only example of acute anterior poliomyelitis (No. 134) was found to have an unusually high percentage of magnesium in the C. S. F. and of post-encephalitis (No. 89) an unusually low one, the significance of these magnesium estimations in the diagnosis of these two diseases cannot yet be absolutely excluded. This is being further investigated. The inclusion or exclusion of these cases affects in no way the conclusions about to be drawn concerning the relations of C. S. F. and serum magnesium.

TABLE I.

No.	Diagnosis.	W. R.		Ca.		Mg.	
		Serum.	C.S.F.	Serum.	C.S.F.	Serum.	C.S.F.
30	General paralysis of the insane		+			4·05	3·26
32	" " " "		+			3·95	3·36
33	" " " "		+			2·96	3·47
34	" " " "		+			3·57	3·24
35	" " " "	+	+			3·28	3·52
40	" " " "		+			2·68	3·16
43	" " " "		+			3·83	3·42
45	" " " "	+	+	12·10	6·36	2·65	3·27
47	" " " "		+			2·62	3·12
48	" " " "	+	+	11·30	6·73	2·74	3·34
49	" " " "	+	+	11·40	6·19	2·80	3·48
53	" " " "	+	+	11·50	8·70	2·73	3·63
54	" " " "		+	11·24	7·21	2·08	3·08
55	" " " "		+	13·17	6·82	2·90	3·10
62	" " " "	+	+	12·32	6·40	3·20	3·70
67	" " " "		+			3·16	3·48
68	" " " "		+			2·95	3·64
85	" " " "	+	+	9·30	5·10	2·88	3·34
86	" " " "	+	+	9·12	4·41	2·95	3·34
90	" " " "	+	+	10·10	6·08	2·64	3·22
91	" " " "	+	+	9·90	6·18	3·00	3·47
92	" " " "	−	+	9·71	5·49	3·07	2·99
95	" " " "		+	9·60	5·88	2·84	3·86
96	" " " "	−	+	10·49	5·59	2·84	3·78
97	" " " "	+	+	10·00	5·78	3·24	3·50
98	" " " "	+	+	10·09	5·78	3·45	3·42
108	" " " "		+	11·07	5·39	2·76	3·30
51	G. P. I. treated with malaria	−	+	13·40	8·20	2·00	3·39
59	" " " "	+	+	11·11	7·63	2·51	3·26
60	" " " "	+	+	12·85	7·26	2·71	3·60
61	" " " "	+	+	11·87	7·26	3·15	3·57
73	Mania	−	−	11·59	5·74	3·40	3·44
118	"	−	−	11·16		2·56	
119	"	−	−	12·35	5·54	2·72	3·36
120	"	−	−	10·58	5·23	2·14	3·40
56	Melancholia	−	−	9·13	6·05	2·42	2·83
74	"		−	12·86	7·54	3·78	3·88
78	"	−		8·62	5·8	2·5	3.19
75	Depression, agitated	−	−	8·80	5·27	3·00	3·44
76	" resistive	−	−	10·68		3·00	
84	Systematized delusions (paraphrenia)	+	−	8·62	5·00	2·72	3·09
93	Depressive psychosis	−	−	10·60	5·98	2·54	3·37
31	Confusional insanity	−	−			3·75	3·32
77	Tabes			11·82	5·48	2·73	3·27
88	"			11·08	5·59	2·78	3·47
100	"			10·00	5·78	2·72	3·50
102	"			9·31	4·80	2·90	3·22
107	"				6·08	2·82	3·10
128	? Tabes	−	−	10·96	4·74	2·74	3·56
109	Epilepsy	−	−	10·68	5·00	2·82	3·14
111	"	−	−	9·70	5·10	2·90	3·32
83	Post-encephalitis (Parkinson's syndrome)			9·04		2·58	
89	" "			10·29	4·62	2·71	2·88
101	Disseminated sclerosis	−	−	10·09	5·29	2·70	3·02
124	" "	−	−	10·86	5·63	2·46	3·40
69	Cerebral arterial sclerosis		−	13·06	7·40	2·68	3·50
52	Cerebral haemorrhage		−	11·70	8·20	2·50	2·96
106	Post. inferior cerebellar thrombosis		−		5·39	2·62	3·16

TABLE I (*continued*).

No.	Diagnosis.	W. R.		Ca.		Mg.	
		Serum.	C. S. F.	Serum.	C. S. F.	Serum.	C. S. F.
94	Spastic hemiplegia		–	11·47	5·88	2·70	3·46
123	Subacute combined degeneration of the cord		–	10·76	5·33	2·57	3·06
105	Meningococcal meningitis	–	–	8·72	5·29	3·28	3·32
104	Aneurism		–	10·19	4·41	3·16	3·63
99	Pituitary tumour		–	9·80	5·39	2·74	3·10
103	Syphilitic myocarditis	+	–	10·39	5·49	2·79	3·90
79	Adenoma of prostate	–	–	9·68	4·68	2·96	3·26
110	Undiagnosed			11·27	5·19	3·05	3·21
129	Sciatica	–	–	11·56	5·33	2·82	3·06
134	Acute ant. poliomyelitis	–	–	9·89	5·85	2·66	3·89

TABLE II.

The Relation between Serum and Cerebrospinal Fluid Magnesium.

Serum mg. per 100 c.c.	No. of cases.	Serum average mg. per 100 c.c.	C. S. F. average mg. per 100 c.c.	Percentage of serum value.
Below 2·6	10	2·37	3·19	134
2·61–3·0	38	2·79	3·37	120
3·01–3·5	11	3·22	3·43	107
Above 3·5	6	3·82	3·41	89

It is evident that the magnesium in the cerebrospinal fluid is on the average remarkably constant, and that the variations that do occur are not due in any material degree to corresponding variations in the serum. As the serum magnesium rises, the cerebrospinal fluid values, expressed as a percentage of the serum magnesium, fall from 134 to 89.

The relationship between the calcium in the serum and cerebrospinal fluid contrasts sharply with that of magnesium. Our results are incorporated in Table III, which shows that the calcium content of the cerebrospinal fluid depends upon the concentration of calcium in the serum. The calcium in the cerebrospinal fluid is on the average about 54·7 per cent. of the serum.

TABLE III.

The Relation between Serum and Cerebrospinal Fluid Calcium.

Serum mg. per 100 c.c.	No. of cases.	Serum average mg. per 100 c.c.	C. S. F. average mg. per 100 c.c.	Percentage of serum value.
Below 9·50	9	8·95	4·92	55
9·51–10·50	15	9·95	5·42	54·5
10·51–11·50	15	11·00	6·02	54·7
Above 11·50	13	12·36	6·73	54·5

As the cerebrospinal fluid is very generally regarded as being formed by filtration processes in the choroid plexus, we felt that a comparison of the cerebrospinal fluid and the ultrafiltrate from the same serum might throw light on the curious relationships of these two ions. The results of these experiments are summarized in Table IV.

TABLE IV.

No.	Diagnosis.	Calcium mg. per 100 c.c. Serum.	C. S. F.	Ultra-filtrate.	Magnesium mg. per 100 c.c. Serum.	C. S. F.	Ultra-filtrate.	Serum protein percentage. Albumin.	Globulin.
113	Normal	10·37		6·17	2·60		2·11		
114	„	10·17		4·84	2·52		1·98		
115	„	9·58		5·81	2·88		2·09		
76	Depressed manic	10·86			3·00		2·26	5·05	2·00
82	Tumour of cord	8·62		4·29	2·82		2·16	5·35	1·68
83	Post-encephalitis	9·04		6·92	2·58		2·08	5·25	2·10
89	„	10·29	4·62	5·20	2·71	2·88	2·05	5·25	1·90
100	Tabes	10·00	5·78	5·59	2·72	3·50	1·88	4·70	2·90
102	„	9·31	4·80	6·17	2·90	3·22	1·81	6·20	1·50
107	„		6·08	4·80	2·62	3·16	2·10	4·45	2·05
101	Disseminated sclerosis	10·09	5·29	4·51	2·70	3·02	1·81	5·25	2·25
124	„ „	10·86	5·63	5·43	2·46	3·40	2·14		
106	Posterio inf. cerebral thrombosis		5·39	6·96	2·62	3·16	2·10	4·90	2·60
108	General paralysis of the insane	11·07	5·39	4·84	2·76	3·30	2·02	5·50	2·55
109	Epileptic	10·68	5·00	5·39	2·82	3·14	1·79	5·25	2·10
123	Subacute combined degeneration of the cord	10·76	5·33	5·63	2·57	3·06	2·04		
94	Spastic hemiplegia	11·47	5·88	5·59	2·70	3·46	2·07	5·30	1·45
128	?Tabes	10·96	4·74	6·32	2·74	3·56	1·90		
129	Sciatica	11·56	5·33	5·33	2·82	3·06	1·96		
	Average	10·33	5·33	5·54	2·71	3·22	2·01		
	Average (serum = 100)	100·0	51·6	53·6	100·0	119·0	74·2		

General Discussion.

We have confirmed the values for normal serum magnesium given by Watchorn (24, 28) by tests made from time to time upon ourselves and other healthy* persons, and suggest that a serum magnesium value higher than 2·65 mg. per 100 c.c. is a very definite sign of ill-health without being diagnostic of any particular disease. As even a common cold may raise the titre, it is not surprising that the majority of our figures, obtained from hospital patients, show values slightly, or even considerably, above this upper normal limit. Cohen (16) obtained an average of 2·56 mg. per 100 c.c. serum for eighteen hospital patients. This is an absolutely normal figure, and it is perhaps rather surprising that he did not obtain a higher average amongst the cases he investigated. In our experience a normal value is rare in such patients. The cerebrospinal fluid values found by us, however, confirm those given by Cohen, our average over a greater number of cases agreeing excellently with his. As we have been fortunate enough to obtain cases giving a wide range of serum values, we feel that the constancy of the cerebrospinal fluid magnesium can be regarded as an established fact. The results obtained by other workers in certain diseases have not been confirmed by us. In our series of manic-depressive cases we have been quite unable to confirm the very

low figures given by Weston and Howard (21). Though one of our cases, it is true, had a low serum value (Case 120, Table I), the cerebrospinal fluid level was normal. The other serum values were normal or raised, and the cerebrospinal values all normal. Neither have we been able to find any definite and consistent differences in general paralysis of the insane, whether treated by malaria or not, as Eisler (20) reports. The difficulty of accepting this worker's figures has already been pointed out. Depisch (3), on the other hand, gives a value for encephalitis which is identical with ours.

Our average serum calcium value lies in the upper limits of the normal range (10·79 mg. per 100 c.c.). Our average cerebrospinal fluid value (6·00 mg. per 100 c.c.) is also slightly higher than that given by other workers, but agrees with the figures given by Cantarow (4) for syphilis ; many of our cases were syphilitic. Halverson and Bergeim (1) give 5·1 mg. per 100 c.c. for tabes dorsalis, but here again our values are somewhat higher (average 5·54 mg. per 100 c.c. for five cases).

Our average value for ultrafiltrable calcium (5·54 mg. per 100 c.c.) is also higher than the normal (4·96) given by Greenberg and Gunther (7), but is in good agreement with the average of our cerebrospinal fluids. It is evident that the calcium in the ultrafiltrates considered as a percentage of the serum calcium is about equal to the cerebrospinal fluid calcium expressed on the same basis. The percentage of magnesium in the ultrafiltrates, however, is always below 100, and generally below 80, whereas that in the cerebrospinal fluid, as we have seen, is generally about 120, and may be as high as 135. In other words, ultrafiltration theories may explain the presence and amount of calcium in the cerebrospinal fluid, *but not the magnesium.*

Summary.

1. The concentration of magnesium in the cerebrospinal fluid is very constant, and usually higher than in the serum. Sixty cerebrospinal fluids give a mean value of 3·33 mg. per 100 c.c., with an average deviation of $\pm 0{\cdot}19$.

2. The percentage of magnesium in the fluid is not altered by the presence of excess of protein, by syphilis, or by wide variations in the serum value.

3. Not more than 80 per cent. of the serum magnesium is ultrafiltrable.

4. Whereas ultrafiltration accounts satisfactorily for the percentage of calcium in the cerebrospinal fluid, the magnesium found there cannot be so explained.

We wish to express our thanks to all those who have in any way helped us to obtain material for this work.

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ARSENOBENZOL PURPURA[1]

WITH A SHORT DESCRIPTION OF FOUR CASES

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The increasing use of the arsenobenzol derivatives in the treatment of syphilis during the past ten years has been associated with not infrequent reports of toxic symptoms attributed to their use. Of these symptoms 'jaundice' and dermatitis are the commonest and best known; among the rarest complications is haemorrhagic purpura.

During the past eighteen months three such cases have been under observation in the Medical Wards of St. Thomas's Hospital, and, owing to the rarity of the condition and the gravity of its prognosis, they appear to be worthy of record. In addition, Professor Elliott of University College Hospital has been kind enough to give us the notes of a hitherto unpublished case. In all cases observation of the blood-picture was kept throughout the disease, and in the fatal cases a complete post-mortem examination was performed.

Although it is possible that other cases have eluded search, we have only been able to find report of fifteen similar cases in the medical literature, recorded with varying degrees of completeness, and these have been used with the four cases presently to be reported in the preparation of this clinical and pathological review of the condition.

Case 1. I. C., an unmarried woman, aged 28, by profession a district nurse, cut her left thumb while cleaning some instruments in September 1926. No primary sore was noticed, but three weeks later she developed a chronic lymphadenitis in the corresponding axilla and later of the cervical glands of the same side. In February 1927 one of the glands was excised for microscopy, and upon the pathological findings she was sent to a tuberculosis sanatorium. While in this institution she developed a sore throat and rash, and a W. R. was found to be positive. She was referred to the Department for Venereal Diseases, St. Thomas's Hospital, at the beginning of March 1928, where the diagnosis of syphilis was confirmed, the W. R. being + +, and treatment commenced. From March to June 1928 she received a course of ten weekly injections each of 0.45 grm. of sulphostab each with 0·3 grm. of bisoxyl deep subcutaneously. The total amount of drugs being: sulphostab 4·5 grm., bisoxyl 3·0 grm. During this course no toxic symptoms were observed, but at the end of it the W. R. was still + +.

[1] Received December 20, 1930.

A rest of two months was allowed, and from August to October 1928 the patient had a further course of nine weekly injections of the same amounts of these drugs, the total being: sulphostab 4·05 grm. and bisoxyl 2·7 grm. The W. R. was then +, and there had been no signs of toxaemia.

On January 18, 1929, a third course was begun on similar lines. She received the sixth and last of these injections at 9 a.m. on March 8, 1929, having received 2·7 grm. of sulphostab and 1·8 grm. of bisoxyl.

Thus from March 1928 till March 1929 she had received 11·25 grm. of sulphostab and 7·5 grm. of bisoxyl.

At 7 p.m. on March 8, i.e. ten hours after the last injection, she noticed that she was bleeding round the roots of several teeth, and on further examination found several haemorrhagic spots on the hard palate and lips. Next day petechiae were present all over the trunk and the proximate parts of both upper and lower limbs. There were no large bruises, nor had any epistaxis, haematemesis, haematuria, or melaena occurred, and apart from slight headache there appeared to be no disturbance of general health.

She was admitted to hospital on March 9, 1929. On examination she appeared to be in good general health. There was no anaemia or jaundice. Pulse-rate 80. Temperature 98·4° F. There was evidence of recent haemorrhage round the roots of several teeth and there were several large petechiae on the hard palate and inside the cheeks and lips, and there were smaller petechiae on the trunk and limbs.

At this time there were no ecchymoses. The retinae showed no haemorrhages. There was no evidence of lymphatic enlargement, the spleen and liver were both impalpable and of normal size to percussion. The heart, lungs, and central nervous system all appeared normal. The urine contained no blood or other abnormal constituents.

Blood Counts.

Date.	R. B. C. (millions).	Hb.	W. B. C.	Platelets.	Polymorphs %.	Eosinophils %.	Basophils %.	Small lymphocytes %.	Large lymphocytes %.	Large hyalines %.
9.3.29	5·6	76	4,160	150,000	81·0	4·0	—	7·0	1·5	6·5
14.3.29	5·02	74	5,480	330,000	74·0	3·5	0·5	10·0	2·0	10·0
18.3.29	6·14	72	12,500	327,000	82·0	2·5	1·0	7·0	3·0	4·5
27.3.29	4·94	82	13,100	265,000	81·0	0·5	0·5	8·0	2·0	8·0
5.4.29	5·28	76	6,880	132,000	78·0	3·0	1·0	6·0	5·0	7·0
22.4.29	4·62	76	8,080	330,000	76·0	3·5	1·0	6·0	5·0	8·0

The progress and treatment of the case were as follows:

March 10. The general condition was the same, but large ecchymoses had appeared upon the inner aspect of the right thigh, the right elbow, left leg, and the left foot. She was given a blood transfusion of 10 oz. during which operation there was an extensive urticarial eruption but no other ill effects.

March 11. No further haemorrhage had occurred. Daily injections of 0·6 grm. of sodium thiosulphate were given daily for six days.

March 12. At 9 a.m. severe epistaxis occurred, and in spite of plugging the nostrils and administration of morphia, oozing continued throughout the night.

March 13. Slight nose bleeding continued but no more cutaneous haemorrhage appeared. The patient was given daily doses of liver powder by the mouth, each dose being the stated equivalent of ½ lb. of fresh liver.

March 14. The nasal plugs were removed without further haemorrhage, but an ecchymosis appeared on the left elbow. The coagulation time on an average of three estimations was 58 seconds (Dale and Lawlaw's method). The bleeding time was 4½ minutes. The tourniquet test was positive. The patient received a second transfusion of 10 oz. No urticaria occurred.

March 15–March 17. No further symptoms arose except pain and tenderness at the site of one of the sodium thiosulphate injections.

March 18. The painful area was red and indurated. The menstrual period commenced, was excessive in amount, and lasted five days.

March 19–March 27. The local tenderness at the site of injection showed no change, and on incision pus giving a pure culture of staphylococcus aureus was obtained.

March 28. Two small epistaxes occurred.

April 4. Repeated epistaxes occurred during the preceding two days. The general condition was good and the abscess had nearly healed.

April 5. Two small epistaxes took place. The tourniquet test was negative.

April 6–April 8. Daily epistaxes occurred. Examination of the nose showed two small ulcers on either side of the septum nasi.

April 12. The menstrual period recommenced, three weeks having elapsed since the last, it was profuse and ceased on the 16th. A small epistaxis took place.

April 29. No further haemorrhage had occurred. The patient was discharged from hospital in apparently normal health.

Since the date of discharge the patient has attended hospital at regular intervals. There has been no further evidence of a haemorrhagic tendency and she is able to carry on her occupation as before her illness occurred.

Case 2. A. S., a married woman, aged 29, came under treatment in March 1929 for syphilis contracted from her husband. No primary lesion was observed, the secondary rash being the presenting symptom. The W.R. was + +.

She was given a course of six weekly injections of novarsenobenzol 0·45 grm. with bisoxyl 0·4 grm. The total quantities were N.A.B. 2·70 grm. and bisoxyl 2·4 grm. After the last injection the face became swollen and red for five minutes and there was severe dyspnoea. Complete recovery took place.

From June 27–August 8, 1929, she received a further course of weekly injections of sulphostab of amounts 0·3, 0·3, 0·45, 0·45 without any bisoxyl. The total amount in this course being 1·5 grm. of sulphostab.

In all she had received 4·20 grm. of arsenobenzol derivatives and 2·4 grm. of bisoxyl.

On August 15 she came to Hospital complaining of severe stomatitis which had been present for several days. She was exsanguinated and bleeding from the gums. Menorrhagia was severe. There was neither haematemesis, haematuria, nor melaena. She refused admission to hospital.

On September 9 she consented to be admitted.

On examination 9.9.29 the patient was exsanguinated and extremely ill. Continuous bleeding occurred from the roots of all the double teeth. The skin was pale but not jaundiced. There were a few petechiae on the trunk and the proximal portions of the limbs, but no ecchymoses. The tourniquet test was positive. Pulse-rate 72—pulse of poor quality. B.P. 95/50. Heart apparently normal. The liver and spleen were impalpable and normal to percussion. There was no enlargement of the lymphatic glands. The urine was normal.

Date.	R. B. C. (millions).	Hb.	W. B. C.	Platelets.	Polymorphs %.	Eosinophils %.	Basophils.	Small lymphocytes %.	Large lymphocytes %.	Large hyalines %.
9.9.29	2·62	55	—	180,000	—	—	—	—	—	—
13.9.29	2·60	65	2,500	—	2·0	—	4·0	82·0	10·0	2·0
16.9.29	1·64	35	3,400	—	—	—	—	—	—	—
20.9.29	1·456	?	2,000	—	0·0	2·0	—	43·0	31·0	24·0

Progress and treatment:

9.9.30. On admission a blood transfusion of 1 pint was given. Urticaria occurred.

10.9.30. Improvement in general condition. Oral haemorrhage ceased.

13.9.30. Oral haemorrhage recommenced.

16.9.30. General condition worse, with severe bleeding from the mouth, and also from the site of blood transfusion. A second transfusion of 1 pint was given during which no urticaria was seen.

17.9.30. Steady deterioration. Haemorrhage from transfusion wound persisted for twenty hours. Excessive oral haemorrhage.

20.9.30. Weakness was extreme. High swinging fever. Respirations rose to 30 and pulse-rate to 150.

21.9.30. The patient died.

Post-mortem report. For the report of the post-mortem examination and the account of the histological changes, we are indebted to Sir Bernard Spilsbury.

The cadaver was well nourished and extremely pale. No jaundice or oedema. Petechiae were present on the neck, right shoulder and thighs, and at the site of injection.

The serous cavities contained a little bloodstained fluid, especially the pelvis, where it appeared to be derived from a haemorrhagic cyst in the left ovary. The lungs were pale and oedematous with fine emphysema. The trachea was normal. The pharynx showed a sloughing gangrenous condition of the left tonsil extending to the pyriform fossa. The teeth showed perialveolar necrosis. The stomach and intestines contained much blood, but were otherwise normal. The bladder contained clear pale urine. There were no petechiae. The uterus was normal. Both ovaries were congested with several haemorrhagic cysts. The liver weighed 39 oz. and was soft and flabby. It was full of air-bubbles due to post-mortem change. The spleen weighed 6 oz. and was congested, firm, and a little spotted. The suprarenals were normal. The kidneys gave a combined weight of 12 oz. They were very pale. The capsules stripped normally, but the cortex was swollen. The heart showed dilatation of both sides. The muscle was pale, but there was no mottling. The coronary arteries were normal. The aorta showed post-mortem and early fatty change.

Histological examination. The heart showed fatty degeneration of the muscle-fibres in some places to an advanced degree. The liver showed marked atrophy of the centre of the lobules. A very few cells in the atrophied zones showed slight fatty degeneration. Neither leucocytic infiltration nor fibrosis was present. Cloudy swelling but no fatty change was present in the kidneys. Stained smears of the bone marrow from rib and femur showed red cells with only occasional nuclei. No myeloblasts, myelocytes, or polymorphs were seen. Sections of bone marrow from the shaft of the femur showed fatty tissue with very few cells, which consisted of nucleated and non-nucleated red blood cells,

rather degenerate cells resembling myeloblasts, and a few large phagocytic cells containing red blood cells and debris.

Case 3. W. M., a married woman, aged 38, first attended in October 1929 for gummatous ulcers of the palate. The W. R. was + +.

From 10.10.29 till 10.1.30 she received ten weekly injections of 0·36 grm. of sulphostab (total 3·6 grm.) and 0·3 grm. bisoxyl (total 3·0 grm.). At the end of this course the W. R. was + +.

From 21.2.30 till 14.3.30 she received pot. iod. gr. xv t.d.s.

From 14.3.30 till 4.7.30 a second course of eight weekly injections of 0·42 grm. of sulphostab (total 3·36 grm.) and bisoxyl 0·25 grm. (total 2·0 grm.) was given. This course was terminated on 4.7.30 when a total quantity of 6·96 of sulphostab and 5·0 grm. of bisoxyl had been given.

On one occasion after these injections the patient experienced a violent sensation of heat and felt very ill. On other occasions she suffered from general aches and pains after the injections. She had never been jaundiced.

On July 9, i.e. five days after her last injection, during which time she had kept quite well, her gums began to bleed. Next day this condition was worse, and on day of admission numerous petechiae and bruises were found on the arms and legs. The menses started on the day before admission—five days before normal, and were excessive in amount. No haemorrhage had occurred from the other mucous surfaces. She felt well in herself. There was no headache.

On examination 11.7.30. The patient was of healthy appearance. Temp. 98·6; P. 84; R. 14. There was old syphilitic scarring of the palate. There was haemorrhage round the molar and lower incisor teeth, and several haemorrhagic bullae on the soft palate, right cheek, and dorsum linguae.

Numerous petechiae were present on the arms, legs, and trunk, and several ecchymoses on the limbs.

Heart: normal. Blood-pressure 120/80.

Lungs: normal.

Abdomen: spleen and liver impalpable and normal to percussion. No enlargement of lymphatic glands.

Urine (catheter specimen): normal.

Central nervous system: normal.

Blood count (1) was recorded on admission.

Date.	R. B. C. (millions).	Hb.	W. B. C.	Platelets.	Polymorphs %.	Eosinophils %.	Basophils %.	Small lymphocytes %.	Large lymphocytes %.	Large hyalines %.
11.7.30	5·76	86	5,800	42,000	62·0	1·0	0·5	—	25·0	11·0
17.7.30	4·76	78	5,600	140,000	60·0	4·0	1·0	—	25·0	10·0

Progress and treatment were as follows:

12.7.30. Oral haemorrhages more marked. Bleeding time: no sign of arrest of bleeding after five minutes. Tourniquet test negative.

14.7.30. Bleeding from gums ceased at 6 p.m. Transfusion of 1 pint of blood was given at 10 p.m. No urticaria occurred.

15.7.30. No further bleeding. Gums still oozed upon brushing teeth. Period still continued. There were some fresh petechiae on the right hand following the application of a tourniquet during transfusion.

17.7.30. No further oral haemorrhage.

21.7.30. Menstrual period ceased. Mouth appeared healthy.

27.7.30. Discharged. No cutaneous haemorrhages were present, and the mouth was healthy. The menstrual period had recommenced on getting up.

This patient has remained fit since discharge.

Case 4. For the clinical notes of this case we are indebted to Professor Elliott.

The patient, a man 55 years old, was found in November 1921 to be infected with syphilis. No other relevant illnesses. He was treated at Moorfields Hospital as follows:

From December 9, 1921, the patient received a course of N.A.B. injections of the following amounts: 0·3 grm. as a first injection followed by seven or nine doses of 0·6 grm., and finally, by two injections of 0·9 grm. The last injection was on February 11, 1922, and no adverse reaction was noticed during the series of injections.

On February 23, the patient noticed red spots appearing on his legs. Next day his gums began to swell, with bleeding from them on the 25th. On the 28th he ceased work, and next day haematuria was noticed.

On March 4, he was admitted to University College Hospital in a seriously ill condition, with fever, generalized purpura, and lethargic prostration. He looked pale, but there was no icterus. The breath was offensive and clotted blood occupied the recesses of the mouth. The left parotid region was swollen. There was blood in the stools as well as in the urine. The plantar responses were extensor on the 5th, and the knee-jerks feeble.

The temperature was 101° on admission, respirations 24, and pulse 90. He became worse and died on March 6, with temperature rising to 105° and respirations to 44, apparently of a terminal broncho-pneumonia. The volume of urine was 28 oz. and 26 oz. respectively in the last two days of life.

On March 6, the following blood count was recorded: red cells 1,810,000 per c.mm.; haemoglobin 38 per cent. Total white cells 1,700 per c.mm. all of which were of lymphoid type, mostly small lymphocytes. No polymorphs were seen after search of three films and no platelets were observed. No polychromasic or other evidence of marrow activity was present.

The post-mortem record of macroscopic appearances was: Numerous minute petechiae in the skin of the body, especially on the legs. Gums dark purple from haemorrhage. Petechial haemorrhages over the heart, the pleural surfaces of the lungs, and the peritoneal surfaces of liver, spleen, and intestines. Haemorrhages in the substance of the liver; and extravasations of blood in the renal sinus, and also in the pelvis and calices. Pancreas and adrenals normal. Haemorrhages on inner surface of stomach, of lower end of oesophagus, and throughout intestines. No record of appearance of brain except that there were no gross lesions in it.

A section of liver gave a moderate Prussian-blue reaction. The central part of the shaft of the femur, by naked-eye examination, showed localized absorption of fatty tissue with localized formation of red marrow in other parts. Section of a rib showed red marrow.

No other gross lesions, except oedema and early broncho-pneumonia in the lungs, were found.

Space forbids a detailed description of the fifteen cases of arsenobenzol purpura which have been found in the literature, but the salient points in the blood-pictures will be referred to in the section on haematology.

The sources from which the remaining cases are derived are as follows: Leredde (1), three cases (two fatal—one of these cases was recorded by Labbé and Langlois (2)); Moore and Foley (3), one case (fatal); Görke (4), two cases

(one fatal); Eschbach (5), one case (fatal); Moore and Kleidel (6), one case (fatal); Davies (7), one case (recovered); Rabut and Oury (8), two cases (both fatal); Smith (9), one case (recovered); O'Leary and Connor (10), two cases (both recovered); Kraemer (11), one case (recovered).

In reviewing the series of cases presented, one is handicapped by two facts. In the first place, each case is lacking in one or more of the clinical investigations necessary for a complete comparison of the condition during life, and in the second place, only five of the nine fatal cases appear to have been submitted to post-mortem examination. For this reason, while a moderately full account can be given of the clinical features of the disease, the pathological aspect is less complete.

1. *Aetiology.* There can be no doubt that these cases of purpura are in fact a result of arsenobenzol therapy. In every case there is a record of the use of one or more of these compounds, usually within an hour or two of the onset of symptoms. Many cases it is true received other medications, such as mercury, bismuth, and potassium iodide at the same time, but by no means all of them. It seems unlikely that the latter drugs played any part in the production of the condition.

The variety of the arsenobenzol compounds used in these cases makes it impossible to attribute the unfortunate occurrences to any one drug in particular. It appears that the power to produce toxic symptoms belongs to them as a group rather than to any one individually.

The quantity administered, and the period of time over which it was given, do not appear to differ from those successfully applied in many thousands of cases, so that the toxic manifestations must be attributed to an idiosyncrasy on the part of the patient rather than to excessive or over-energetic therapy.

The total number of cases available for analysis is nineteen. In view of the enormous number of patients treated annually by arsenobenzol compounds, the extreme rarity of the condition is hardly open to dispute.

Of nineteen cases recorded, ten were males and nine females.

2. *Mortality.* Of nineteen cases, ten ended fatally and nine recovered, giving an apparent mortality of 53 per cent. It seems unlikely that this gives quite a true estimate of the prospect of life in a case developing purpura during the course of treatment with arsenobenzol, as it is probable that more benign cases than fatal ones have gone unrecorded.

3. *Prodromal symptoms.* Ten out of the nineteen cases appear to have had prodromal symptoms before the onset of purpura. These symptoms varied greatly in their nature, the commonest being jaundice, headache, transitory erythemata, and rigors.

Several writers comment upon the frequent occurrence of prodromal symptoms which they consider an absolute contraindication to further arsenobenzol treatment.

4. *Clinical symptoms and signs.* In all cases, whether prodromata had occurred or not, the onset of purpura was dramatically sudden. In seventeen

cases haemorrhages from the oral mucous membrane was a prominent and often the first haemorrhagic symptom. This varied from simple oozing round the teeth, with submucous haemorrhages, to a necrotic angina. Cutaneous haemorrhages occurred in fifteen cases and consisted of petechiae, ecchymoses, haemorrhage at the site of needle punctures and in response to increased capillary pressure from a torniquet.

Haemorrhage from other mucous surfaces, such as haematemesis, haematuria, melaena, or menorrhagia were present in twelve cases, of which six were fatal, showing that they are of no greater import than cutaneous and oral haemorrhage.

Pyrexia was a constant feature, and rigors were present in several cases.

A profound anaemia characterized those cases which proved fatal, and will be referred to in more detail later.

Two cases (1 and 8) died in a manner suggestive of cerebral haemorrhage.

Enlargement of the liver was noticed in three cases (3 and 5) and jaundice in three cases (1, 3, and 6).

It is impossible to say whether the jaundice or hepatic enlargement was connected with the purpura as cause and effect, or whether they were both results of the same toxaemia. The latter hypothesis seems more likely. In no case was the spleen reported as palpable. The lungs, kidney, and brain showed no abnormality, except such as resulted from haemorrhage.

Haematology. On the fifteen cases found from a study of the literature, records of blood examinations are given in ten, and these are shown in the accompanying table. It will be seen that a progressive diminution of both red cells and haemoglobin occurs especially in severe and fatal cases—in some instances to a profound degree. There is a tendency for the colour-index to remain high and a study of the table shows that in some cases it becomes greater than unity. Of the ten cases shown in the table, a leucopenia of varying degree was present in seven, of which six proved fatal. In addition, the second and fourth, described by us, also showed a leucopenia and was fatal. Accompanying the leucopenia, there is always an absolute and relative decrease of polymorphonuclear cells—indeed, in the most severe cases, very low figures are found. In Case 4 not a single polymorphonuclear cell was found. An estimation of the blood-platelets was made in seven of the fifteen cases quoted from the literature, and in all the cases described by us, a thrombocytopenia was found in each of the eleven cases. In seven cases it was associated with a leucopenia.

Although undoubtedly a not inconsiderable amount of the anaemia which is found in these cases is caused by actual loss of blood from haemorrhage, a consideration of the blood-picture as a whole shows that an aplasia of the marrow is the important underlying factor of the disease. The blood-pictures correspond with those found in primary purpura whether due to essential thrombocytopenia or to aplastic anaemia between both of which conditions intermediate cases occur.

An examination of the table shows that from the practical point of view,

it is the result of the examination of the total and differential leucocyte counts which is most illuminating in estimating the severity of the disease. The result of platelet estimation is less important. Of 10 cases showing a leucopenia, only 2 recovered, and in them the differential leucocyte count was more favourable than in the remaining 8 cases. The bleeding time was prolonged in 6 out of 7 cases estimated, and the coagulation time increased in 4 out of 6 cases.

Morbid anatomy and pathology. Of 10 fatal cases (8 obtained from the literature and 2 described by us) 6 were submitted to post-mortem examination. Rabut and Oury found in their cases evidences of repeated haemorrhages from the stomach which microscopical examination showed to contain a large lymphocytic infiltration in the mucous membrane in the inter-glandular spaces suggesting an inflammatory change. There was an increase of free cellular elements in the spleen which consisted chiefly of myelocytes, but a number of nucleated red cells and a few macrophages were also found. Polymorpho-nuclear cells were absent. Little change was found in the liver and no mention was made as to the condition of the bone-marrow. Görke found at autopsy in the fatal case which he recorded a profound anaemia and haemorrhages into the skin and endocardium. The red marrow was yellowish-red in colour, and microscopically showed a marked reduction of erythroblasts and myelocytes. No megakaryocytes were found. Moore and Foley found in their case small haemorrhages into the kidneys, under the mucous membrane of the bladder, and into the right suprarenal body. There was slight jaundice. The liver and spleen were normal. Microscopical examination showed small haemorrhages throughout the lungs, and a definite aplasia of the bone-marrow. A more detailed description of the post-mortem appearances including those found in the bone-marrow, is found in the case reported by Moore and Kleidel, in which the microscopic changes were described by McCallum. Extensive subcutaneous and subserous haemorrhages, submucous haemorrhages of stomach, intestines, and liver, and haemorrhagic nephritis, aplastic bone-marrow, lobular pneumonia, oedema of lungs and arteriosclerosis were found. The mucous membrane of the mouth was ulcerated, and a purulent material was oozing from the region of the gums. The bone-marrow from the ribs was red. The cavity of the femur contained a large amount of fat in which an occasional collection of active marrow was seen. Microscopical sections from the marrow of the femur showed it to be almost entirely composed of fat with occasional collections of cells, the type of which was difficult to identify but appeared to be an atypical form of myeloblast. The same cells were found in large numbers in the reticulum of the spleen, and between the venules and also the connective tissue of the liver, but to a less extent.

Treatment: Little can be said with regard to the treatment of this condition. Blood transfusion, and the administration of liver extract may perhaps be considered as the most hopeful means at our disposal, but it appears to be very doubtful if either has any real influence upon the ultimate course of the disease.

Serial Blood Counts.

Author.	Termination.	Date.	Red (millions).	Hb.	C. I.	Whites.	Polymorphs %.	Lymphocytes %.	Basophil cells %.	Platelets.
Leredde (case reported by Labbe and Langlois)	Died	—	1·6	—	—	4,650	30·0	25·0	—	—
Moore and Foley	Died	22.3.17	2·9	35	0·6	2,400	31·0	26·5	—	—
		24.3.17	3·8	52	0·68	1,060	44·5	51·5	—	—
Görke (Case No. 1)	Died	14.3.19	1·6	30	0·97	2,500	20·0	75·0	—	22,000
		17.3.19	1·4	20	0·8	2,100	—	—	—	16,000
		19.3.19	1·03	15	0·7	1,100	12·0	87·0	—	11,000
		19.3.19	0·9	13	0·6	600	—	—	—	—
,, (Case No. 2)	Recovered	3.4.19	3·5	65	0·9	2,700	46·0	38·0	—	48,000
		11.4.19	4·28	70	0·8	2,600	48·0	42·0	—	36,000
Moore and Kleidel	Died	5.6.19	3·83	75	0·97	1,600	17·0	79·0	—	none seen
		7.6.19	4·12	81	0·98	1,000	15·0	78·0	—	,, ,,
		12.6.19	4·11	74	0·9	800	9·0	89·0	—	48,000
		18.6.19	3·87	81	1·01	550	4·0	94·0	—	28,000
		20.6.19	2·99	76	1·1	900	5·0	92·0	—	28,800
Rabut and Oury (Case No. 1)	Died	7.2.22	3·2	75	1·17	1,000	51·0	30·0	—	50,000
		10.2.22	2·5	70	1·4	1,000	—	—	—	—
,, ,, ,, (Case No. 2)	Died	19.3.22	2·36	—	—	1,200	—	—	—	—
		22.3.22	1·8	—	—	1,500	55·0	14·0	—	60,000
O'Leary and Connor (Case No. 1)	Recovered	29.4.24	3·79	61	0·8	14,000	97·5	1·0	—	—
		30.4.24	—	—	—	4,300	90·0	6·0	0·5	104,000
		1.5.24	3·91	65	0·8	4,400	73·5	17·0	2·5	98,000
		2.5.24	—	—	—	5,900	72·0	16·5	2·0	80,000
		8.5.24	3·84	58	0·7	6,900	60·0	29·5	7·0	180,000
,, ,, ,, (Case No. 2)	Recovered	4.6.24	4·21	76	0·9	7,600	—	—	—	—
		2.2.25	3·92	68	0·8	8,000	88·5	7·5	—	154,000
		3.2.25	3·76	65	0·7	7,300	—	—	—	44,000
		4.2.25	4·21	70	0·8	7,500	—	—	—	740,000
		5.2.25	—	—	—	—	—	—	—	900,000
Kraemer	Recovered	29.6.25	4·0	75	0·9	8,000	—	—	—	—
		2.7.25	2·76	69	1·25	27,000	79·0	15·15	—	—
		3.7.25	2·39	49	1·04	—	—	—	—	—
		4.7.25	2·44	65	1·32	—	—	—	—	—
		6.7.25	2·68	60	1·13	—	—	—	—	—
		7.7.25	2·28	45	0·99	6,660	—	—	—	—

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CRITICAL REVIEW

THE METABOLISM OF CALCIUM AND PHOSPHORUS AND THE PARATHYROIDS IN HEALTH AND DISEASE[1]

By DONALD HUNTER

Contents

	PAGE
Introduction	394
Normal Metabolism of Calcium	394
Absorption of Calcium	394
Excretion of Calcium	395
Calcium Content of Blood	396
Calcium in Tissues	397
Functions of Calcium	397
Normal Metabolism of Phosphorus	398
Plasma Inorganic Phosphorus	399
Functions of Phosphorus	399
Phosphatases	400
Distribution of Phosphatases	400
Plasma Phosphatase	400
Bone Phosphatase	400
Phosphatases in Intestinal Mucosa and Kidney	401
Effects of the Parathyroid Hormone	401
On the Blood	402
On Calcium Excretion	402
On Phosphorus Metabolism	403
Over-dosage with Parathyroid Extract	404
Parathyroid Tetany	404
Post-operative Tetany	404
Spontaneous Hypo-parathyroidism	406
Lesions of Ectodermal Tissues	406
Source of Available Calcium	407
Effect of Parathormone on Bones	407
Effect of Calcium Content of Diet on Bones	408
Madder Experiments on Growth of Bones	408
Madder Experiments on Source of Available Calcium	409
Generalized Osteitis Fibrosa of von Recklinghausen	409
Relation of Parathyroid Tumour to Changes in Bone	410
Hyper-parathyroidism	411
Pathogenesis of Generalized Osteitis Fibrosa	413
Focal Osteitis Fibrosa	415
Haematogenous Myelomatosis	415
Effects on Calcium Metabolism of Thyroxin and Thyroid Disease	417
Thyroid Treatment of Parathyroid Tetany	418
Action of Thyroid and Parathyroid Contrasted	418
Radiographic Studies of Bones in Exophthalmic Goitre	419
Osteoporosis in Exophthalmic Goitre	420
Irradiated Ergosterol	420
Effects of Over-dosage	421
Method of Irradiation	422
Rickets	423
Osteomalacia	424
Clinical Features	425
Pathogenesis	425
Economic Factors	426
Antenatal Rickets	427
Influence of Diet on the Structure of Teeth	428
Hunger Osteopathy	428
Styfsiekte, or Stiff-sickness of Cattle	430
Late Rickets	431
Coeliac Rickets	431
Idiopathic Steatorrhoeas of Adults	432
Renal Rickets	432
Osteitis Deformans	433
Osteogenesis Imperfecta	434
Otosclerosis	435
Storage and Excretion of Lead	435
Effect of Ammonium Chloride on Elimination of Lead	436
Effect of Parathyroid Extract in Lead Poisoning	436
Storage of Other Elements in Bone	437
Use of Calcium Salts in Therapeutics	437
Need for a Diet Adequate in Calcium	437
Tetany	438
Lead Poisoning	438
Colic	439
Acute Necroses of the Liver	439
Oedema and Inflammatory Exudates	440
Erythema Pernio, Asthma, and Chronic Ulceration	440
Milk Fever of Cows	441

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Introduction.

THE subject of the metabolism of calcium and phosphorus is so vast that, in a review of the literature such as is here contemplated, many of the published papers must necessarily be omitted. So far as possible the more important and suggestive papers have been referred to and suffice, it is hoped, to indicate the known facts and the directions which must be taken by future work. Those aspects of the subject have been chosen which seem to illuminate the field of clinical medicine to the neglect, it is feared, of those which interest the chemist. There are many points on which no work seems to have been done, and the statements of different workers, especially those whose results were obtained before the introduction of accurate methods, are often contradictory. Progress has been made by investigators in experimental pathology, morbid anatomy, histology, physiology, chemistry, pharmacology, medicine, dietetics, surgery, ophthalmology, radiology, gynaecology, agriculture, and veterinary pathology. Yet in spite of this increasing recognition of the importance of calcium and phosphorus in the economy of animals and plants, our knowledge of many aspects of the subject is scarcely more than primitive.

Normal Metabolism of Calcium.

Calcium is an element essential to the life of plants and animals. In the form of carbonate and phosphate it constitutes two of the most important soil compounds. The carbonic acid of soil water converts insoluble limestone and calcium phosphate into soluble acid salts. These are in part removed from the soil by the plant, for in the germination of seeds and in the growth of plants calcium exerts a specific action. Different species of plants and different parts of the same plant contain different amounts of the element. Seeds, roots, and tubers are poorly supplied, but the green parts are especially rich, and green food is therefore the greatest source of calcium for herbivorous animals. Man derives calcium principally from milk, cheese, butter, eggs, green vegetables, and nuts.

Absorption of calcium. Calcium exists in our food in both organic and inorganic combination. It is probable that digestive changes convert it entirely into the inorganic form, so that it is absorbed as calcium salts partly or completely ionized. Nevertheless calcium salts given by the mouth, whether soluble or insoluble, appear to be absorbed only with difficulty. It is important to remember that an excess of calcium in the diet is desirable, for the very good reason that interaction with carbonates of the digestive juices reconverts some of the ingested calcium into insoluble carbonate, which escapes absorption and is lost in the stools.

The daily calcium requirement of an adult is between 0·4 and 1·0 grm., and the latter figure can be regarded as allowing the necessary margin for safety (Sherman, 1920). Until the growth of the skeleton is complete the daily requirement exceeds this figure.

It has been claimed that calcium chloride is absorbed with much greater ease than calcium lactate. There is no doubt that administration of calcium chloride often produces a greater rise in the serum calcium than is the case with calcium lactate, but this is explained by the fact that the ingestion of calcium chloride in large doses produces an acidosis which is itself responsible for part of the rise in the serum calcium.

Excess of certain mineral constituents in the diet may be detrimental to calcium assimilation. The action of potassium and magnesium in this respect is little understood, but the influence of a large excess of phosphate is to be expected, since calcium phosphate is so insoluble. A great deal of work has been done on the relationship between calcium absorption and the sugar content of the diet. It would seem that the addition of 25 per cent. of lactose to the diet increases the absorption of calcium (Bergeim, 1926).

Studies of the effects on calcium metabolism of the addition of fat to the diet have been pursued for many years. It was found that some fats were efficacious in improving calcium absorption whereas others were not. Attention was therefore turned to the vitamin content of fat as a possible explanation (E. Mellanby, 1918). It was then found (McCollum, 1922) that cod-liver oil was equally effective, whether administered fresh or after oxygenation for twelve hours, whereby its content of vitamin A had been entirely destroyed. It was obvious, therefore, that the effects were not due to vitamin A, and since they were apparently not due to the fat itself, it was necessary to postulate an antirachitic vitamin distinct from vitamin A. More recent work on the effects of ultra-violet irradiation has led to the view that certain fats contain a special antirachitic substance, vitamin D. This is more resistant to oxidation than is vitamin A, and can be produced in many otherwise inactive fats, such as olive oil, by exposure to ultra-violet light. It is now known that vitamin D is a derivative of ergosterol, or some closely related sterol (Rosenheim and Webster, 1927), and that as such it can be synthesized in the skin. It seems to be the main factor governing the absorption of calcium, but whether or not it directly affects calcium utilization in the tissues remains for future metabolism experiments to decide.

Excretion of calcium. It is generally accepted that calcium is eliminated by the large intestine and to a less extent by the kidney. The average concentration of calcium in the saliva is 9 mg. per 100 c.c., in the gastric juice 6 mg., in the pancreatic juice 7 mg., and in gall-bladder bile 11 mg. By the use of Thiry-Vella pouches in dogs it has been shown that calcium is eliminated to a much greater extent by the lower intestinal mucosa than by the upper (Walsh and Ivy, 1927). Thus daily washings with distilled water of a pouch of the upper jejunum yielded up to 1·2 mg. of calcium, the corresponding figure for the lower ileum being 8·5 mg. and for the colon 15 mg. It follows, then, that on a normal diet the faecal calcium consists of the unabsorbed surplus together with re-excreted calcium.

The urinary excretion of calcium varies from 0·1 grm. per day on a low

calcium diet to 0·5 grm. on a normal diet. It is, perhaps, not sufficiently well recognized that acid-forming diets increase the urinary excretion of calcium. For example, it has been shown (Aub, 1928) that a diet consisting of bread, meat, rice, fats, macaroni, and sweets, and excluding milk, green vegetables, and fruits, may give rise in the body to about 700 c.c. N/10 excess acid. Such a diet may double the normal elimination of calcium in the urine and may cause a marked increase in the titratable acidity and ammonia output. When such an acid-forming diet is neutralized with an equivalent amount of sodium bicarbonate, there is no longer either an increased titratable acidity, or an increased ammonia and calcium elimination in the urine. This indicates that the increased excretion is caused purely by the excess of acid in the diet.

When acidosis is deliberately brought about by large doses of ammonium chloride, a very great increase of calcium excretion may be produced. For example, in a normal subject on a low calcium diet taking 12 grm. of ammonium chloride a day, Aub found that the urinary calcium was increased in three days from 0·1 to 1·1 grm., while the faecal calcium remained essentially unchanged. The degree of response varied with the individual, but there was always an increased calcium output.

The effects of the parathyroid and thyroid hormones on calcium excretion will be discussed later.

Calcium content of blood. Very wide variations are found in the figures given for the calcium content of whole blood, serum, plasma, and corpuscles. To no small extent this is due to untrustworthy methods. The evidence is almost conclusive that the red cells of the blood contain no calcium: at the most, but minute traces can be present. Most workers state that the calcium content of the plasma is practically identical with that of the serum. There is evidence, however, that in true plasma, obtained by rapid cooling and centrifuging of the blood drawn under paraffin, the concentration of calcium is 10 to 15 per cent. higher than in the corresponding serum (Stewart and Percival, 1928).

In estimating the blood-serum calcium, the Kramer-Tisdall method as modified by Clark and Collip (1925) gives results with an average error of 2 per cent. and a maximum error of 5 per cent. The normal figure by this method varies between 9·0 and 11·0 mg. per 100 c.c.

Now in the cerebrospinal fluid the figure is only 5 to 6 mg. per 100 c.c., and in agreement with this difference it has been found that serum and plasma calcium is but little more than half diffusible. It is obvious, therefore, that calcium is present in blood plasma in more than one form. Actually it is believed to be present in three forms, namely, un-ionized, non-diffusible organic compounds approximately 45 per cent., un-ionized, diffusible, or dialysable inorganic compounds approximately 35 per cent., and calcium ions approximately 20 per cent. Electrometric determinations are responsible for the last figure, and the methods for the determination of the diffusible calcium are unsatisfactory. The methods of dialysing the serum against distilled water or a solution of known calcium concentration are slow and inaccurate. In collodion

filtration the results may be affected by the time of filtration and by the pressure employed.

Certain physiological variations in the serum calcium are of interest. Thus it has been found to be higher during the first few days of life and during the suckling period than in adult life. The claim that the serum calcium rises before menstruation and then rapidly falls is based on the faulty methods of twenty years ago, and modern work fails to confirm the observation. The best attested alteration in the serum calcium occurs during pregnancy and is doubtless due to the drain on the maternal tissues to meet the growing demands of the foetus. Bogert and Plass (1923) found that the average calcium content of the serum was 9·1 mg. per 100 c.c. for 23 women at the time of labour, and 10·2 mg. for 12 normal non-pregnant women.

It has been shown that the blood calcium of certain birds increases very considerably at the period of ovulation. Thus in female pigeons a rise in blood calcium begins 123 hours before the beginning of the formation of an egg-shell (Riddle and Reinhart, 1926). Subsequently, during a period of from three to five days, these birds withstand without trace of adverse effect a hypercalcaemia up to 20 mg. per 100 c.c. Similarly the female cod in the spawning season has a blood calcium varying from 12·7 to 29 mg. per 100 c.c., whereas the corresponding figure in the male lies between 9 and 12·5 mg. (Hess, 1927). This calcium is probably required for the elaboration of the eggs, which are especially rich in that element.

Calcium in tissues. Speaking approximately, for there are no reliable figures, calcium is distributed evenly throughout the soft tissues in amounts comparable to those found in the blood plasma. Thus muscle contains 6·5 mg. per 100 grm. When, however, we come to the skeleton the corresponding figure is about 10,000 mg. Calcium phosphate constitutes 80 per cent. of the mineral content of bone. There are in addition calcium carbonate, which makes for greater hardness, magnesium phosphate, and traces of fluoride, the last being present in greatest amount in the enamel of teeth. The protective shells of invertebrates consist almost entirely of calcium carbonate, but traces of phosphate are invariably present, and there is good ground for belief, that the presence of phosphate is absolutely essential both for shell and for bone formation. The calcium in milk is about equally divided between organic and inorganic constituents, the organic compound, calcium caseinogenate, being non-diffusible. The activity of the mammary gland is responsible for a concentration of calcium which averages 42 mg. per 100 c.c. in human milk and 120 mg. in cow's milk.

Functions of calcium. The most obvious function of calcium in the body is, of course, the formation of bone. It has perhaps been insufficiently emphasized that the skeleton of the mammal is not only a supporting structure, but is also a reservoir of calcium and phosphorus. Even after full growth is complete, bone salts are being continuously removed and renewed, and they are not once and for all laid down and fixed. And since bone is the only considerable reservoir of calcium in the mammal, the skeleton can be drawn upon not only

for the skeletal needs of the foetus where there is a dietary deficiency of calcium, but, apparently often as a normal procedure, as in the production of milk. The hen, on a diet deficient in calcium, can draw on its skeleton for the calcium of the egg-shell. Further, the skeleton is not the only structure which acts as a reservoir for calcium. There is experimental evidence that the shell of the egg can be dissolved by the carbonic acid produced by the growing embryo, to yield a soluble calcium salt for the needs of that embryo: 80 per cent. or more of its calcium requirements are provided from the shell (Cameron, 1926).

Apart from the growth and maintenance of the skeleton, calcium plays an important part in the blood and tissues by maintaining along with other ions a balanced system which determines the degree of irritability of muscle and nerve. In this way calcium ions help to control the heart beat, the contractility of plain and striped muscle, and the transference of impulses at the neuro-muscular junctions and through synapses. In general it may be stated that calcium ions play an important part in lessening the irritability of the tissues containing them.

Nevertheless wide variations from the normal can exist without apparent interference with such functions. Thus in post-operative tetany and infantile tetany the serum calcium may drop to 6 mg. per 100 c.c. before any symptoms or signs of lack of calcium are observed. Conversely, in parathyroid over-dosage and in spontaneous hyper-parathyroidism symptomless hypercalcaemia has been observed, the serum calcium values being 19·8 and 16·7 mg. per 100 c.c. respectively.

An important function of calcium is to aid in the coagulation of shed blood. Mellanby (1908) showed that the action of calcium is specific, since, although salts of magnesium, strontium, and barium will, in the presence of thrombo-kinase, convert prothrombin into thrombin, none of them compares in potency with calcium. It follows that any manipulation which depletes the blood of calcium ions, such as the addition of oxalate or citrate, prevents clotting. The delayed coagulation time in haemophilia may be due, theoretically, to a variation of any one of the factors concerned in clotting, but there is no evidence to indicate a calcium defect.

Cases of fatal haemorrhage after operations for obstructive jaundice may perhaps be explained by removal of calcium ions which have combined with bile salts. Little or no satisfactory work is to be found on this subject.

In the clotting of milk, calcium ions are essential in the process of converting casein into insoluble calcium caseinate, the clot mesh.

Normal Metabolism of Phosphorus.

Phosphorus is ingested in the food as nucleoprotein (meat), phosphoprotein (milk), lecithin (egg yolk, liver), and as inorganic phosphate. It is found in the blood, not only in the inorganic state, but also in combination with a variety of organic radicles. The organic compounds are acid-soluble 'ester phosphorus',

and alcohol-ether soluble 'lipin phosphorus'. It is, perhaps, not sufficiently realized that less than one-twelfth of the total phosphorus is present as inorganic phosphate.

Plasma inorganic phosphorus. The plasma and corpuscles contain equal amounts of inorganic phosphorus, so that the results of analyses may be expressed as milligrammes of phosphorus per 100 c.c. of whole blood or plasma. Most of the early work on blood phosphate must be accepted with caution, for it was not known before 1914 that the distribution of phosphorus changes when blood is allowed to stand. Once the corpuscles have been laked, the liberated organic esters are very rapidly hydrolysed by the plasma phosphatase, and the concentration of inorganic phosphate rises rapidly. However, with adequate precautions, using the method of Briggs (1924), the experimental error should not exceed 2 per cent.

In health the level of inorganic phosphate in the blood varies between 2·5 and 3·5 mg. phosphorus per 100 c.c. In children, where ossification is more active, readings up to 5 mg. per 100 c.c. are found. The blood obtained from the umbilical cord at birth may contain as much as 6 mg. per 100 c.c. The metabolism of phosphorus is closely interwoven with that of calcium, and many of the observed fluctuations in the blood phosphate can be accounted secondary to changes in calcium. There is often a reciprocal relationship between calcium and inorganic phosphorus in the blood, though this is only approximate and does not apply where absorption of phosphorus is defective.

Functions of phosphorus. Phosphorus compounds take part in at least four important metabolic processes. They are in some way essential to the storage or utilization of carbohydrate, they enter into the chemical changes which precede the contraction of muscle, they are concerned with acid-base equilibrium, and they are essential to the deposition of bone.

The physico-chemical mechanism of ossification is little understood. Freudenberg and György (1920) have suggested that the cartilage protein forms a compound of calcium by virtue of its acidic groups, that the resulting compound, having now a preponderance of basic groups, combines with phosphate ions, and that the calcium-protein-phosphate complex so formed breaks down with deposition of insoluble calcium phosphate and liberation of the original protein. Holt, La Mer, and Chown (1925), from their work on the physical chemistry of calcium phosphate solutions, conclude that the blood serum is to be regarded as a supersaturated solution of tertiary calcium phosphate, and that the plasma bathing the bone matrix, where solid calcium phosphate is present, readily gives up its surplus and so enables the bone to grow.

The interesting theory of Robison (1926) as to the possible significance of bone phosphatase in the process of ossification has been supported by much experimental evidence. The work of Kay (1929, 1930) on plasma phosphatase, in the study of certain metabolic diseases of bone, has provided circumstantial support for Robison's theory from an entirely different quarter.

Phosphatases.

For our knowledge of the distribution and possible functions of phosphatases in the body we are indebted to Robison, Kay, and collaborators. Phosphatases are enzymes which hydrolyse phosphoric esters such as glycerophosphate and hexosephosphate. Many of these esters form soluble calcium salts. Such esters are widely distributed in the tissues, mainly inside the cells. Two such esters occur in mammalian red cells, and a phosphoric ester, hydrolysable by animal phosphatases occurs, in small quantities only, in human plasma. Phosphatases also hydrolyse pyrophosphates which are said to occur in muscle tissue.

Distribution of phosphatases. Phosphatases are very widely distributed in mammalian tissues. In the human adult the epithelial portion of the intestinal mucosa is richest in phosphatase, the whole kidney next. There is more in the cortex of the kidney than in the medulla, and more in the mucous membrane of the intestine than in the submucosa. Adult bone contains phosphatase very unequally distributed, the enzyme being present mainly below the periosteum. Per unit weight of bone, young growing bones contain much more phosphatase than adult bones. Again the distribution is very irregular, the enzyme being present mainly in the zone of provisional calcification and in the periosteum. Foetal bones contain a still higher proportion of phosphatase per unit weight of bone. The concentration of phosphatase in and about the cells of the ossifying zone in foetal cartilage is probably greater than that of phosphatase in any other tissue. The foetal kidney, on the other hand, contains considerably less phosphatase than the kidney a few days after birth.

Plasma phosphatase. In 1929 Kay published a method for estimating the activity of the phosphatase in the plasma. He expresses this enzyme activity in terms of the number of milligrammes of phosphorus liberated as inorganic phosphate from excess of sodium β-glycerophosphate in forty-eight hours at 38° C. and at pH 7·6 by 1 c.c. of plasma. Under these conditions the average value for normal plasma is 0·15 mg. In young infants the figure is higher. In certain generalized diseases of bone the phosphatase of the plasma frequently rises to ten or twenty times the normal. Very high figures are constant in osteitis deformans. In generalized osteitis fibrosa, in secondary carcinomatosis of bones, in rickets and in renal rickets high figures have been found (Kay, 1930). On the other hand, in focal osteitis fibrosa the figures are normal (Hunter, 1930).

Bone phosphatase. There seems little doubt that phosphatase plays a part in the chain of events by which the deposition of calcium phosphate in growing bones is brought about. Robison's hypothesis may be briefly stated as follows: the osteoblasts and hypertrophic cartilage cells secrete a very active phosphatase, which, by hydrolysing the phosphoric esters of the blood, brings about a local increase in the concentration of phosphate ions. The solubility product of tertiary calcium phosphate is thereby exceeded, and deposition of

this salt occurs in the ossifying zone. The enzyme probably plays a part also in the maintenance and repair of bone in the adult.

The evidence in favour of this hypothesis may be briefly outlined as follows:

1. Phosphatase is present in the growing bone in greatest amount in those areas in which deposition of calcium phosphate is proceeding most rapidly.

2. It can be demonstrated *in vitro* that a growing bone split longitudinally is still capable of the deposition of calcium phosphate from a solution of a soluble calcium phosphoric ester salt such as calcium hexosemonophosphate or calcium glycerophosphate, and that deposition occurs mainly in the cells in the zone of provisional calcification.

3. Phosphatase appears in cartilage simultaneously with the appearance of centres of ossification.

4. There is no phosphatase in cartilage which is not ossifying.

5. There is a substrate for the enzyme present in red cells and also in circulating plasma.

6. In certain generalized diseases of bone, and, almost without exception, in no other disease, the plasma phosphatase is raised.

This last finding establishes yet another strong correlation between bone maintenance and phosphatase. It also tends to reinforce the opinion which has been growing of late, that to understand the biochemistry of bone formation, maintenance, and pathology, emphasis should be laid as much on the metabolism of phosphorus as on that of calcium.

Phosphatases in intestinal mucosa and kidney. Phosphatases in the intestinal mucosa hydrolyse the phosphoric esters in the food. All the evidence at present available indicates that phosphoric esters taken by mouth are absorbed as inorganic phosphates. Any phosphoric ester in the food is probably completely hydrolysed by the phosphatases of the intestinal juice and the mucosa before absorption into the blood-stream. The rate of hydrolysis of various phosphoric esters is not, however, the same, so that the more resistant will probably be hydrolysed farther down the intestine than the less resistant. Milk, for example, in addition to caseinogen, contains calcium phosphate in at least seven other forms of combination. These compounds of milk will be hydrolysed and their components absorbed at different levels in the intestinal tract. The peculiar ease with which the calcium and phosphorus of milk are taken up from the intestine is probably dependent upon these facts. The kidney phosphatase possibly plays some part in the secretion of inorganic phosphate in the urine.

Effects of the Parathyroid Hormone.

The parathyroid glands exert a specific effect upon calcium metabolism. The pioneer work of MacCallum and Voegtlin (1909) demonstrating a reduction of serum calcium in dogs after parathyroidectomy has been abundantly confirmed. It is well established that this condition is relieved by the administration

of calcium salts. The idea that it is due to guanidine intoxication remains unsupported by adequate evidence.

Effects of parathyroid extract on the blood. The view that calcium deficiency is the direct cause of post-operative tetany is considerably strengthened by the work of Hanson (1924) and Collip (1925), who isolated an active extract of the parathyroid gland. Injections of this substance abolish tetany in parathyroidectomized dogs, the serum calcium being restored to normal. Administration of Collip's extract (parathormone) to normal dogs raises the serum calcium above normal to an extent so nearly proportional to the dose as to afford a means of standardization.

During certain observations on patients suffering from chronic lead poisoning Hunter and Aub (1926) had the opportunity of investigating the effect of parathormone on the chemistry of the blood and on calcium excretion. These patients were kept on a constant diet containing an inadequate amount of calcium. Parathormone was given by intramuscular injection either twice or three times a day. In five patients out of six it was found that, by giving an average dose of 55 units daily, the blood calcium could be increased to 13 mg. per 100 c.c. or more within eight or nine days. The most effective method was to give three doses a day and to increase the daily dosage continuously from say, 20 to 100 units by adding 10 units daily. This gradual elevation of the calcium level in the blood is the most dramatic effect of parathormone, but its extent varies in different individuals. It was found to be more marked when calcium lactate was added to the diet.

Effects of parathyroid extract on calcium excretion. Before the isolation of potent extracts of the parathyroids, erroneous conclusions had been arrived at as to the effect of thyro-parathyroidectomy on calcium excretion. Thus the statement of MacCallum and Voegtlin (1909) that after this operation dogs showed an increased excretion of calcium has not been corroborated. Cooke (1910) repeated their work and was unable to find any change in the excretion of calcium after parathyroidectomy. In spite of this contradictory report, the statement of MacCallum and Voegtlin became widely accepted. Thus arose the idea (Salvesen, 1923) that parathyroidectomy was associated with a lowered threshold for the excretion of calcium by the intestines. It was supposed that the resulting drain on calcium kept the blood-serum calcium at a low level. Greenwald and Gross (1925) demonstrated that the true conception of the relation of the parathyroid glands to calcium excretion is the very reverse of that above stated. By a technique which eliminated many sources of error incurred in previous animal experiments, they demonstrated that dogs after parathyroidectomy actually showed a *decrease* in the excretion of calcium. In a later series of experiments (1926) they were enabled, by the use of Collip's parathyroid extract, to approach the problem from the opposite point of view. They injected normal dogs with the extract, and found that the increased concentration of calcium brought about in the blood-serum was followed by an increase in the excretion of calcium.

During their investigations on patients with chronic lead poisoning Hunter and Aub were able to observe the effects of parathormone on calcium excretion when the intake was known. Their patients were placed on a low calcium diet, so that a negative calcium balance already existed. In all their observations parathormone definitely increased this negative calcium balance, the average increase being 53 per cent. The increase was roughly proportional to the dosage given. When parathormone was discontinued the calcium output did not immediately drop to normal but remained somewhat raised for periods of from three to six days. The increase of calcium output was very much more marked in the urine, the increase of faecal excretion being negligible.

In considering the physiological action of the parathyroids, the source of these large amounts of calcium appearing in the urine is of fundamental importance. Hunter and Aub considered it justifiable to infer from their results, as Greenwald did from his animal experiments, that parathormone, administered during a deficient calcium intake, causes *increased* excretion of calcium salts from the bones.

Effects of parathyroid extract on phosphorus metabolism. Though the most dramatic effects of parathormone are on the blood calcium and calcium excretion, there is evidence (Aub, 1928) that its primary effect is on phosphorus excretion. Parathormone abruptly increases the urinary phosphorus excretion without affecting the faecal excretion. At the same time the level of the inorganic phosphorus in the blood is reduced. When parathormone injections are stopped the urinary phosphorus excretion rapidly falls to a level below that found before. These changes are more rapid than those just described in the case of calcium metabolism. They are also greater than can be explained by a theoretical calculation of the phosphorus liberated with calcium and nitrogen (from calcium phosphate and protein respectively), so that the excreted phosphorus is evidently derived partly from the body fluids.

These remarks apply only to the primary effect of parathormone on phosphorus metabolism. If parathormone is continued in large doses a secondary effect appears later. It was first emphasized by Collip that when a certain critical level of serum calcium has been reached, following parathormone injections, the blood phosphorus rises abruptly. This may be due to an alteration in kidney function resulting from the high serum calcium, for the non-protein nitrogen of the blood also rises. Thus a later effect of parathormone on phosphorus metabolism is brought about, which is exactly opposite to the primary effect.

There are several other observations which lend support to the view that the primary action of parathormone is on phosphorus. Greenwald (1925) has shown that there is a marked retention of phosphorus in the first two days after parathyroidectomy. This suggests the possibility that the bad effect of a meat diet on parathyroid tetany may be due to its high phosphorus content. Collip (1926) showed that, following parathyroidectomy in the rabbit, the serum phosphorus rose without much change in the serum calcium, and that parathormone,

if administered directly following operation, would prevent this rise. He stated that 'these observations tend to emphasize the importance of phosphorus in relation to the pathogenesis of tetany'. Further, tetany has been produced in dogs by intravenous injection of phosphates (Binger, 1917) and likewise by administering large doses of phosphates by mouth (Salvesen, 1924).

Effects of over-dosage with parathyroid extract. The work of Collip (1925) on dogs brought to light a new entity—hypercalcaemia. This condition has since been found to occur in man, both spontaneously and as the result of parathyroid over-dosage. In Collip's observations on dogs no ill-effects were noted if the dosage of parathyroid extract was only sufficient to cause a rise in the serum calcium to 14 or 15 mg. per 100 c.c. Large doses of the hormone, however, administered five times in the twenty-four hours often caused death within forty-eight hours of the first dose. Though in such cases the blood calcium rose to 20 or 21 mg. per 100 c.c., Collip made no claim that the hypercalcaemia was the immediate cause of death. In describing the condition of these animals he states that 'the clinical manifestations of hypercalcaemia in dogs appear to be loss of appetite, dullness, drowsiness verging on coma, general atonia, and a failing circulation. The animals are also obviously dehydrated, the blood becomes very concentrated, and it becomes a matter of great difficulty to secure serum from blood samples for analysis even when a high-power centrifuge is used. Immediately after death the blood in the heart and great vessels forms a firm clot.' Complete investigations of the blood chemistry showed that the inorganic phosphorus rose in the later stages of hypercalcaemia and that there was nitrogen retention. Thus in one dog the blood at death had a phosphorus content of 13 mg. per 100 c.c. and a urea content of 111 mg.

Severe hypercalcaemia has been produced inadvertently in the human subject. In one such case the serum calcium was raised to 19·8 mg. per 100 c.c. and remained at this level for forty-eight hours. The levels of plasma phosphorus and non-protein nitrogen were also raised. The changes in the physical properties of the blood observed by Collip in dogs suffering from parathyroid over-dosage were absent. Throughout the whole time the patient remained up and about, and, except for slight nausea and loss of appetite, appeared to be normal (Hunter and Aub).

Prolonged over-dosage with parathormone in the dog may give rise to metastatic calcification in the kidneys, lungs, myocardium, and gastro-intestinal tract (Hueper, 1927).

Parathyroid Tetany.

Parathyroid deficiency occurs in clinical medicine both as post-operative tetany, following operations upon the thyroid, and as spontaneous hypo-parathyroidism, which is analogous to myxoedema. Both conditions are rare, and metabolic studies have shown them to be of great interest.

Post-operative tetany. Owing to the fact that radical thyroidectomy is not

a common practice in this country, post-operative tetany is rare. It is not so in all countries, especially in those where operations for endemic goitre are common. In the United States, where it is customary to remove nine-tenths of the thyroid gland for exophthalmic goitre, post-operative tetany is more often seen than it is here. It is for this reason that Lahey (1926) examines as a routine the specimens removed at operation, and, if any tissue suggesting parathyroid is found, he transplants it into the sterno-mastoid muscle, preferably reserving a portion for histological examination.

Fortunately, chronic post-operative tetany is often a mild disease easily controlled by calcium therapy. As an instance, however, of the severe and ultimately fatal outcome which is sometimes seen in post-operative tetany, the case of Aub (1926) may be quoted.

Case of post-operative tetany (Aub). The patient was a girl who had been examined at the age of 17, having a history of a goitre, first noticed three years before. Tremor, tachycardia, and slight exophthalmos were found. The basal metabolic rate was plus 45 per cent. Later in the same year two extensive operations were performed constituting total thyroidectomy. Two months after the second operation attacks of difficult breathing occurred, and were later accompanied by severe carpopedal spasm and sometimes by convulsions. Two years later cataracts began to appear in both eyes, necessitating bilateral lens extraction.

On examination nine years after thyroidectomy, the skin was found to be dry and the axillary and pubic hair scanty. No thyroid tissue could be palpated in the neck. Chvostek, Trousseau, and Erb signs were positive. The blood calcium was 4·3 mg. per 100 c.c., and the inorganic phosphorus 5·6 mg. per 100 c.c. The basal metabolic rate was minus 18 per cent. Fifteen units of parathormone given daily raised the blood calcium to 6·7 mg. per 100 c.c. in eighteen days. When it reached this level the attacks of difficult breathing and tetany disappeared.

The output of calcium on a known low calcium intake was estimated during this treatment, and found to be excessively low. In fact the output was almost the same as the intake and much less than that of normal individuals on the same diet. This occurred in spite of the fact that she was being given 15 units of parathormone daily, which should have caused an increase in her calcium excretion. These figures for calcium excretion are lower than those found in any other disease, and indicate that the low blood calcium is due, not to an increased permeability of the kidney or intestinal mucosa to calcium, but rather to a diminished endogenous calcium metabolism and a diminished demand upon the calcium reserves in the bones.

Unfortunately, the effect of parathormone gradually diminished in this patient. Initially the blood calcium had been raised by a dose of 15 units, whereas after some months doses of 100 units had no effect at all. The results to the patient were disastrous, for the persistent low blood calcium was accompanied by severe attacks of tetany, associated with bronchial spasm, laryngeal spasm, and unconsciousness, and in such an attack she died.

Aub (1928) interprets this phenomenon as an 'immunity' to parathyroid extract. He states that:

'Unfortunately, parathormone has several disadvantages, which make its long-continued clinical use unsatisfactory at present. First, its action varies markedly in different individuals. Thus, one normal individual will show a marked reaction, while another will get no effect from a similar dose of the

same extract. Second, and more important, there is an immunity to the drug which has developed in many of our cases after a few weeks of treatment. When such an immunity appears, even very large doses of parathormone exert no influence on blood calcium or phosphorus. This loss of potency has lasted in one case for a full year, and is dependent upon a resistance to the preparation and not to a drainage of the storehouse of calcium, for an increased calcium excretion followed the administration of ammonium chloride after parathyroid had proved inert. This is apparently the only active principle of a gland of internal secretion which develops such an immunity, and this effect may possibly be dependent upon the protein still present in the extract.

Spontaneous hypo-parathyroidism. It has now been definitely shown that just as myxoedema is, as a rule, a spontaneous hypo-thyroidism, so an analogous condition of the parathyroids exists. This is exactly similar to post-operative tetany, except that it is of spontaneous origin. Albright and Ellsworth (1929) have recorded such a case.

Case of spontaneous hypo-parathyroidism (Albright and Ellsworth). A boy of 14 was admitted to hospital for the relief of tetany. At the age of 8 attacks of laryngismus had occurred, followed the next year by carpopedal spasm. At the age of 10 Chvostek and Erb signs were positive, the blood calcium being 4·9 mg. per 100 c.c. and the phosphorus 10·4 mg. The boy then became worse, so that at the age of 14 he was having each day about fifteen attacks of carpopedal spasm, sometimes with momentary loss of consciousness. The blood calcium was still low and the phosphorus high. The basal metabolic rate was minus 6 per cent. Following the administration of parathormone there was complete relief. The blood calcium was raised to 16·2 mg. per 100 c.c. and the phosphorus dropped to 4·7 mg. However, after discontinuing the injections of parathormone, symptoms returned in one week. Seen later, at the age of 15, the boy again had tetany; the blood calcium was 5·3 mg. per 100 c.c., and the phosphorus 10·8 mg. The urine was normal. Radiograms of the bones showed no abnormality. Ophthalmoscopic examination revealed a subcapsular lenticular opacity in the right eye and a few lenticular opacities in the left.

In this case there are many features which strongly suggest parathyroid deficiency. The low serum calcium with high plasma phosphorus is comparable to the findings in post-operative tetany, and is the exact converse of what has been found in parathyroid over-dosage and hyper-parathyroidism. The administration of parathormone relieved the tetany, raised the blood calcium, and lowered the phosphorus. Finally, the occurrence of lenticular opacities is comparable to what is found in post-operative tetany.

Lesions of ectodermal tissues. Cataract, brittleness and ridging of the nails (Jacques, 1928), loss of hair (Sainton and Péron, 1922), and defects in the enamel of teeth, giving rise to several transverse ridges one above the other: all these defects in ectodermal tissues have been described in tetany. None of these changes is common, but the first is met four times as frequently as any of the other three.

The association of cataract with tetany was first recorded about fifty years ago. It has been described in endemic tetany (Hesse and Phleps, 1913), post-operative tetany, rickets, and spontaneous hypo-parathyroidism. In 1906 Erdheim observed the occurrence of cataract in rats six months after

experimental parathyroidectomy. Thyro-parathyroidectomy in dogs may produce opacities in the lens within periods varying from three months (Dragstedt, 1924) to two years (Edmunds, 1915). Since 1924 it has been possible (Knüsel, 1924; Goulden, 1928), by means of the slit-lamp, to demonstrate opacities in the lens where no visual disturbance exists.

The Source of Available Calcium.

Studies of the metabolism during fasting show that the only fixed base which is drawn from body tissues is calcium. Thus, in starvation, sodium and potassium are retained, whereas calcium is excreted continuously from the bones. Is the mechanism which protects the sodium and potassium of the tissues sufficiently perfect to spare the bone in such a way as to leave its function as a supporting structure unimpaired? Certain experimental, radiological, and pathological evidence suggests that it is—suggests, in fact, that the spongiosa of bone acts as the storehouse of readily available calcium, and that the corticalis is at first spared in the process of calcium mobilization.

Effect of parathormone on bones. Experimental observations on this problem were made by Bauer, Aub, and Albright (1929) working with rabbits and cats. Rabbits were injected with parathormone in increasing doses until they were receiving eight units per day. After ninety-one days they were killed together with controls. Each rabbit had received approximately 500 units of parathormone and this had raised the serum calcium to about 15 mg. per 100 c.c. Radiograms showed diminished density of the bones compared to the controls. The long bones, when sawn longitudinally and incinerated, showed that a great number of trabeculae of the spongiosa had disappeared, but no gross change could be seen in the corticalis. No histological observations were made.

Jaffe and Bodansky (1930) produced typical osteitis fibrosa cystica in three dogs which were injected for five to six months with gradually increasing daily doses of parathormone. At the end of the experimental period they were receiving twenty units daily. These authors state that the dogs with the more pronounced lesions showed:—(1) resorption of the existing spongy and cortical bone, (2) invasion of the enlarged Haversian spaces and of the marrow canals by fibrous tissue, (3) the presence of Howship's lacunae, containing osteoclasts, on the walls of the Haversian spaces, on the inner and outer surfaces of the compacta, and on the surfaces of the spongy trabeculae, (4) new bone formation, as a substitute for the original lamellar bone, and (5) cysts and haemorrhages in the marrow cavity. Some of the bones were deformed, particularly those of the forelegs. The bone changes were generalized, and gave rise to stunting of growth. The production of osteitis fibrosa cystica was enhanced in the dogs by feeding them on a low calcium diet. By this means larger doses of parathormone could be given without danger of hypercalcaemia. That the changes observed could not be attributed to calcium deficiency alone was evident from examination of bones of control dogs kept for months on

a low calcium diet. These animals developed osteoporosis, which is histologically quite different from osteitis fibrosa cystica. With relatively large doses of parathormone, Jaffe, Bodansky, and Blair (1930, 1931) produced generalized osteitis fibrosa in young guinea-pigs.

Effect of calcium content of diet on bones. In cats changes in the spongy bone have been brought about by diet alone (Bauer, Aub, and Albright, 1929). Five cats were placed on a high calcium diet consisting of milk, and four on a low calcium diet consisting of meat, fresh uncooked liver, and water. At the end of several months the left foreleg was amputated at the shoulder-joint, and the diets were reversed. After a similar period of time the animals were killed, thus allowing comparison of the humerus representing the period of high calcium diet with that of the period of low calcium diet. In this ingenious manner each animal served as its own control, and factors such as age, sex, activity, and season did not enter into the results obtained. These experiments showed that the trabeculae of spongy bone in adult cats are diminished on a low calcium diet and increased on a high calcium diet. The authors state that 'no gross change in cortical thickness was demonstrable'. The histological nature of this resorption and apposition of bone was not investigated.

Madder experiments on growth of bones. It was probably Antonius Mizaldus (1566) who first noticed the red coloration of the bones of animals fed with madder. This phenomenon was not known in England until the year 1736. In the summer of that year a young surgeon, John Belchier, was entertained to supper by a calico printer in the City of London. His host was economical in his affairs and was in the habit of feeding his pigs on the madder-soaked bran from his dye-vats. The result was that Belchier noticed that the pork served at table contained bone dyed red. Immediately afterwards he began experimenting on hens by forcibly feeding them on madder. One died after sixteen days, and he found the bones, even those of the densest structure, stained deep red.

The osteogenetic function of the periosteum was discovered by du Hamel (1742) using this technique. He fed birds and animals alternately on madder diet and on ordinary food. He then demonstrated in the bones successive red and white layers or rings, the area formed latest being on the surface of the bone immediately under the periosteum. Only bone freshly deposited during the madder feeding was stained bright red, though all bone might assume a pale pink colour.

In 1764 John Hunter used the method to prove his theory of bone growth. He fed growing animals on a madder diet for a month, then killed some of them, and kept the others for a further month on ordinary diet. Twenty preparations from these experiments are preserved in the Museum of the Royal College of Surgeons in London. Unfortunately the colour has faded from them, though some paintings have survived in better condition. Examination of these paintings, especially those of the mandible of a pig, fully bears out his statement: 'In the formation of a bone, ossification begins in a spot and

gradually increases. By feeding an animal on madder, it is shown that, while bony matter is deposited on the outside of the bone, the absorbents are removing it from the inner side, otherwise the bone would become heavy and clumsy, and unfit for motion; therefore, as the bony matter which was deposited becomes useless, nature removes it by absorbents' (MS. Lectures).

Now the colour-bearing substance of madder is a glucoside of alizarin, and in recent years experimenters have used alizarin in place of madder. For intra-muscular or intravenous use in animals sodium alizarin sulphonate has been used, since it is more soluble.

Madder experiments on source of available calcium. Bauer, Aub, and Albright (1929) used the dye as a method of tracing the deposition of calcium following a prolonged period of calcium deficiency. Unlike previous experimenters with madder they were not studying the process of growth, and they therefore worked with adult animals. Nine cats were kept on a low calcium diet for eighty-two days. It was thought that this was long enough to deplete the spongy bone of its trabeculae. The cats were then placed on a high calcium diet and sodium alizarin sulphonate was given by intramuscular injection. After varying lengths of time on this treatment the cats were killed and their bones sawn longitudinally and cleaned by digestion in pancreatic solution at pH 8·3 for thirty-six hours. The bones of six cats killed on the fifty-fifth day of the high calcium diet showed the trabeculae of the spongiosa stained deep red while the corticalis showed no trace of the dye. This suggests that the calcium stored on the high calcium diet was deposited in the spongy bone, and that the corticalis had not been depleted by the low calcium diet.

Generalized Osteitis Fibrosa of von Recklinghausen.

Generalized osteitis fibrosa is a disease which progresses with pain, fractures, and disabling deformities and is usually fatal. There is widespread pathological resorption affecting all the bones. In addition there are multiple foci of osteitis fibrosa with or without benign giant-celled tumours and cysts. It is a disease entity distinctly different from focal osteitis fibrosa. In the latter there may be one or more focal lesions, the essential point being that outside these lesions we have evidence that all bony tissue is normal.

In a Festschrift written in 1891 in honour of the seventy-first birthday of Virchow, von Recklinghausen gave the first accurate description of the disease entity which now goes by his name. His contribution to the Festschrift is very involved, for he describes more than one bone disease. There can be no doubt, however, that his Cases 5 and 7 constitute the discovery of generalized osteitis fibrosa. It is important for us to notice that he went to the trouble of describing two cases of puerperal osteomalacia (Cases 8 and 10) in order to place on record that 'so many facts differentiate Case 7 from true osteomalacia'. He describes his Case 7 as 'osteitis fibrosa with marked bone softening and multiple osteosarcomata'. The patient was a man of 40, thought to be suffering

from osteomalacia. There was a history of eighteen months' bone pain with bowing of the bones and multiple spontaneous fractures. At necropsy the bones were soft and deformed so that with a saw they cut like rotten wood, and the shafts could be cut with a knife using moderate force. All the bones in the skeleton were affected, and seemed histologically to be formed of a tough connective tissue. Brown-red projecting tumours were found in the fibula, iliac crest, and upper and lower jaws. In our subsequent knowledge of this disease there is ample clinical and pathological evidence to establish the benign nature of these giant-celled tumours. The cells themselves are similar to the osteoclasts normally present in Howship's lacunae.

Thirteen years after von Recklinghausen first described generalized osteitis fibrosa, an important step was made towards solving the problem of its aetiology. This was a description by Askanazy in 1904 of a case of generalized osteitis fibrosa associated with a parathyroid tumour. The patient was a woman aged 51, complaining of pains in the limbs, and suffering from multiple spontaneous fractures. At necropsy, to the left of the left thyroid lobe there was a tumour which looked almost like a second left thyroid lobe. A parathyroid origin of this tumour was suspected. The femur was fractured in three places, and all the bones of the skeleton cut easily with a knife. Microscopically the process of destruction of old bone was carried out by numerous osteoclasts lying in Howship's lacunae. Sometimes small bony particles were seen surrounded by giant cells, and occasionally only the osteoclasts were seen, singly or in groups, free in connective tissue. Since its significance was scarcely suspected, the parathyroid tumour mentioned by Askanazy in this case passed unnoticed. However, the description by Erdheim in 1907 of three cases of osteomalacia with enlargement of the parathyroids called forth many other observations of bone disease associated with hyperplasia or tumour formation in the parathyroid glands.

In 1925 Hoffheinz, rejecting all cases where the enlargement of the parathyroids was indefinite or inadequately described, collected from the literature 45 cases with measurable enlargement of one or more parathyroids. Of these, 27 were associated with definite bone disease, including 17 of generalized osteitis fibrosa, 8 of osteomalacia, and 2 of rickets. He quoted increases of size up to 7 by 2·5 by 1 cm. The histological changes were either those of hyperplasia or of adenoma, and it is important for us to notice that sometimes more than one parathyroid gland was affected. In cases of generalized osteitis fibrosa renal calculi have commonly been observed, and areas of metastatic calcification have been found in the lungs, stomach, kidneys, and myocardium (Dawson and Struthers, 1923).

Relation of parathyroid tumour to changes in bone. Amongst pathologists a difference of opinion arose as to whether the parathyroid tumour was primary or secondary in relation to the bone disease. Erdheim himself defended the view that the disease of the skeleton was the primary factor, and that skeletal decalcification created such a demand for calcium that a

compensatory hypertrophy of the parathyroids occurred. Anatomical evidence against this view was found in the fact that, in generalized osteitis fibrosa, hypertrophy or tumour formation was often confined to one parathyroid, the others remaining apparently normal. On account of Erdheim's investigations the whole question was repeatedly discussed at scientific meetings in Vienna. As early as 1915 Schlagenhaufer at such a meeting, raised the question as to whether it was not justifiable to attempt the extirpation of a parathyroid tumour in cases of generalized osteitis fibrosa. Maresch supported this suggestion, but it was not until 1926 that Mandl of the Vienna school first performed this operation. In view of the Vienna controversy it is of great interest that he decided to explore the neck only after treatment by parathyroid transplants and parathyroid tablets had failed to relieve the symptoms. The patient was a man of 38 with a history of pains in the pelvis and lower extremities for five years. Radiograms showed osteitis fibrosa of femora, pelvis, tibia, and ischium. Spontaneous fracture of the femur occurred, and he became unable to stand or sit. Four parathyroid bodies from an accident case were transplanted into the abdominal wall. No improvement occurred. It was therefore decided to explore the neck, though no tumour could be felt. A parathyroid tumour (2·5 by 1·5 by 1·2 mm.) was removed at operation. Pains in the bones disappeared a few days after operation. The urinary calcium excretion dropped to one-eighth of the pre-operative value. Three and a half years after the operation he still had no pains in the bones, and walked with a stick. The serum calcium at that time is reported as 13 to 14 mg. per 100 c.c., and no increase in density of the X-ray shadows of the bones had occurred.

Hyper-parathyroidism. We now turn to the biochemical aspect of this problem. In 1926 Hannon, Shorr, McClellan, and Du Bois investigated the case of a man of 34 with the symptoms and signs of a generalized disease of the skeleton. Radiograms showed an extensive decrease in the density of the shadows of bones, and a large cyst in the right femur. There was a high blood calcium (serum Ca 15·3 mg. per 100 c.c.) and a low blood phosphorus (plasma inorganic P 1·4 mg. per 100 c.c.). In 1929 Richardson, Aub, and Bauer investigated the same case, and found that the urinary output of calcium and phosphorus on a low calcium diet was six to seven times greater than was found in normal individuals under identical conditions. They found that these changes in metabolism were equivalent to those of a normal individual receiving 100 units of parathormone daily. It was, therefore, reasonable to suppose that this patient was suffering from hyper-parathyroidism. Exploration of the neck revealed no tumour, but this does not mean that no such tumour existed, for we now know that parathyroid tumours may be deeply situated behind the trachea or even in the mediastinum. It was the study of this case and the use of Aub's methods which led to the discovery of many cases of hyper-parathyroidism in the United States and in this country. Meanwhile in Germany, Austria, and Holland the work of Mandl was producing the same effect.

Satisfactory proof of hyper-parathyroidism now exists in 32 cases of

generalized osteitis fibrosa. In 22 of these a parathyroid tumour was removed by operation, in 2 cases two parathyroid tumours were removed, and in 5 cases no parathyroid tumour was found at operation. The remaining 3 cases were not operated upon, but proof was obtained by autopsy of a parathyroid tumour in 2 cases (Lambie, 1927; Ask-Upmark, 1930), and of two parathyroid tumours in the remaining case (Hunter, 1931, Case 1). The condition is reported twice as frequently in women as in men, the commonest ages being 30 and 55. Pain in the bones, osteoclastomata (Barr, 1929; Wilder, 1929) and spontaneous fractures (Snapper, 1929; Hannon, 1930) were common. Thirst and polyuria occurred in 5 cases (Amberg, 1930; Disqué, 1930), renal calculi in 10 cases, and haematuria in 1 case (Quick and Hunsberger, 1931). Occasionally renal colic was the presenting symptom (Léri, 1930; Hunter, 1931, Case 3). Hypotonicity of muscles was described in 7 cases (Barr, 1929; Compere, 1930). In only 5 cases was the parathyroid tumour palpable in the neck (Wilder, 1929; Barr, 1930, Case 2). In 4 cases exploration of the neck revealed no tumour. The largest tumour removed measured 7·5 by 5·0 by 1·8 cm. and weighed 26·2 grm., and yet it had not been palpable in the neck owing to its situation behind the trachea (Hunter, 1931, Case 4). The size of the tumour bears no relation to the severity of the bone lesions, for in the most severely crippled patient the tumour measured 2·3 by 1·5 by 0·9 cm. and weighed only 1·3 grm. (Hunter, 1931, Case 2). Nausea and vomiting, sometimes with abdominal cramps, have been described (Ball, 1930; Pemberton and Geddie, 1930). Wasting is common in advanced cases. In those cases where radiograms are mentioned there was greatly diminished density of bone shadows. This is best demonstrated by contrast with the bones of a control subject of the same age, sex, and build, exposed simultaneously on the same negative. Sometimes there was radiological evidence of cysts, but these only rarely expanded the corticalis. The serum calcium figures varied between 12·6 and 23·6 mg. per 100 c.c., the plasma phosphorus between 1·0 and 2·7 mg. Where the plasma phosphatase was estimated (9 cases) it was invariably high. The output of calcium in the urine varied from a slight increase to eight times the normal figure.

In the majority of cases pain in the bones was abolished immediately after operation, and the mechanism of this is difficult to conceive. Decrease in size of osteoclastomata within a few weeks after operation has been twice recorded (Barr, 1929; Hunter, 1931, Case 2). Restoration to normal of the menstrual function has also been observed. In 3 cases removal of the tumour promptly abolished polydipsia and polyuria (Boyd, 1929). In one case renal calculi began to break up a few weeks after operation and were passed into the bladder. In many cases the levels of the serum calcium and plasma phosphorus and the excretion of calcium in the urine were restored to normal. Sometimes there was temporary hypocalcaemia and even oliguria, with subnormal excretion of calcium in the urine (Gold, 1928). In all five cases where it was recorded after operation the plasma phosphatase remained high; in one of these it showed

no alteration even twelve months later. Latent tetany after operation was common, and manifest tetany often occurred, with marked variations in severity. It was fatal in one case only, where two parathyroid tumours were removed (Beck, 1928). Nevertheless removal of two parathyroid tumours is not necessarily fatal, nor even necessarily accompanied by post-operative tetany (Hunter, 1931, Case 4). In the case recorded by Snapper (1929) tremor and acute mania occurred three weeks after operation, at a time when the serum calcium had dropped to 6·6 mg. per 100 c.c. The condition was completely relieved in three days by the use of parathormone injections in conjunction with a preparation of calcium given intravenously. This latter procedure must undoubtedly be regarded as the essential treatment of severe post-operative tetany following removal of a parathyroid tumour. The post-operative treatment should include a high calcium diet and ultra-violet irradiation as routine procedures.

Symptomatic improvement almost always occurs after removal of a tumour. Not only is pain in the bones abolished, but there is marked gain in weight, and many crippled patients have been able to dispense with sticks and crutches. In one case, however, pain in the bones was not entirely abolished eighteen months after operation (Wilder, 1931). Where no parathyroid tumour was discovered removal of a normal parathyroid had no good effect in two cases (Barrenscheen and Gold, 1928; Wendel, 1930), but removal of two normal parathyroids led to considerable symptomatic improvement in another (Bauer, Albright, and Aub, 1930). Some authors claim that an increase in density in the radiographic shadows of bones was to be seen in their cases a few months after operation. It is of great interest that three and a half years after operation Mandl could demonstrate no such change in his case. Should there be special reasons contra-indicating operation upon the neck, or should no tumour be found, the patient may be treated with irradiated ergosterol in the hope of increasing the apposition of bone (Regnier, 1929). In at least one case good evidence has been obtained of the effect of such treatment in increasing the density of bone as judged by radiograms (Snapper and Boevé. 1931).

Pathogenesis of generalized osteitis fibrosa. Generalized osteitis fibrosa is characterized by changes in the skeleton, enlargement of one or more parathyroid glands, hypercalcaemia, and an increased excretion of calcium in the urine. The changes in the skeleton are lacunar resorption, apposition, fibrosis of marrow, and the formation of osteoclastomata and cysts. Lacunar resorption is the predominant change. There is a general osteoporosis, which varies in degree in different places. Apposition, however, does not cease. Where present it is usually abnormally active, and most of the bone formed is non-lamellar. The exceptional rapidity of apposition explains (Turnbull, 1930, 1931) the abnormal depth of many of the osteoid zones; there is no osteomalacia in the strict sense. Fibrosis of the marrow is a conspicuous feature. It is very widespread, but not universal. It is intimately connected with bone, appearing upon its surface, and is closely associated with activity of resorption and

apposition. In places it is focal and fills bays and spaces in bone, ensheathes trabeculae, or encloses groups of trabeculae in the spongiosa; in other places, where resorption is greater, it extends through the corticalis or through both corticalis and spongiosa. In the latter case there may be a focal expansion of the bone. The close relations to bone and to active changes in bone suggest that it is simply an expression of excessive activity of the osteogenetic marrow (Turnbull, 1931). All resorption and apposition necessitates a cellular proliferation of the osteogenetic marrow. A similar fibrosis is seen in florid rickets where there is a very active formation of osteoid tissue. If the fibrosis of the marrow is inflammatory, its intimate relation to bone requires the cause of the inflammation to lie in what appears initially to be perfectly normal bone. In view of the changes in the calcium metabolism and the skeleton in patients, and in animals given parathormone experimentally, the excessive activity of the osteogenetic marrow can be attributed primarily to excessive stimulation of resorption by parathormone and secondarily to excessive stimulation of apposition by strain and stress upon the weakened bone. The osteoclastomata can be explained as areas of marrow stimulated to exaggerated osteoclastic activity; they have been observed to disappear after removal of enlarged parathyroid glands (Barr, Bulger, and Dixon, 1929; Hunter, 1931). Jaffe and Bodansky (1930) and Jaffe, Bodansky, and Blair (1930, 1931) to have caused typical generalized osteitis fibrosa in dogs and guinea-pigs by administration of parathormone.

If, however, the skeletal changes are secondary to hyper-parathyroidism the cause of the latter remains unexplained. According to Turnbull (1931) the enlargement of the parathyroid glands appears to be due to functional hyperplasia and not to autonomous new growth. The glands are occupied by cells which, apart from giant nuclei and multiple nuclei, correspond in structure and size to those found in normal glands. Giant and multiple nuclei are not evidence of neoplasm; they are found in abnormal activities of glands, for instance, in the thyroid in Graves' disease. There is no abnormality in the architecture of the glands except such alterations in the boundaries of the acini as result from enlargement of the acini by hyperplasia of their cells. The predominant type of cell varies in different cases. In one case (Hunter, 1931, Case 4) a very large gland was occupied almost completely by pale oxyphile cells, whilst another gland was less enlarged, and showed small acini of principal cells obviously in process of conversion into massive acini of pale oxyphile cells. Here the evidence of functional hyperplasia appeared conclusive.

If, then, the changes in the bones are the result of functional hyperactivity of the parathyroid glands, the position is similar to that in Graves' disease, in which the cause of the abnormal activity of the thyroid is obscure. Parathyroid hyperplasia is known, however, to occur secondarily to abnormal conditions of the skeleton. It has been seen, for instance, in the disturbance of calcium metabolism constituting osteomalacia (Erdheim, 1907; Hoffheinz, 1925), and even in secondary carcinomatosis of bones (Klemperer, 1923) and

haematogenous myelomatosis (Barr and Bulger, 1930; Bulger, Dixon, and Barr, 1930). This favours the view that generalized osteitis fibrosa is a primary disease of bone to which parathyroid hyperplasia is secondary. In view of the changes in calcium metabolism, the effects of operation, and the experiments of Jaffe and Bodansky (1930), it is impossible to believe that the secretion from the enlarged glands causes no skeletal alteration in generalized osteitis fibrosa. Alterations due to hyper-parathyroidism may, however, in this condition be superimposed upon a primary disease of bone. In Paget's osteitis deformans there is no evidence of hyper-parathyroidism, but exactly similar histological changes occur in the skeleton, except that the interplay of excessive resorption and apposition is more chronic, and apposition predominates (Turnbull, 1931). This does not prove that the fibrosis in both generalized osteitis fibrosa and Paget's osteitis deformans is not simply an expression of hyperactivity of the osteogenetic marrow, but it does suggest caution in attributing to hyper-parathyroidism all the skeletal changes in generalized osteitis fibrosa. In either case, whether the hyperplasia in the parathyroids is secondary to an obscure bone disease or is primary but of unknown cause, it is obviously necessary to be guarded in expressing an opinion upon the ultimate results of extirpation of enlarged glands.

Focal Osteitis Fibrosa.

Of much more common occurrence than the generalized disease is focal osteitis fibrosa. This is a condition affecting one or more bones, usually not disabling, of slow progress, and showing a tendency to become arrested. It occurs chiefly in adolescence, and is often symptomless until spontaneous fracture occurs. In seven cases investigated by Hunter (1930) the serum calcium and plasma phosphorus and phosphatase were normal. In two of these cases the calcium balance was normal, a finding in striking contrast to that of the generalized disease. Taken in conjunction with the normal blood chemistry the finding of a normal calcium metabolism is of far-reaching importance. Supported as it is by the normal density of the radiographic shadows of bones, it is evidence strongly against hyper-parathyroidism. It is of vital importance in such cases to realize that, although many bones are affected, the condition is totally different from the generalized disease and that exploration of the neck is clearly unjustifiable.

Haematogenous Myelomatosis.

In the light of recent knowledge the history of haematogenous myelomatosis assumes some importance. For obvious reasons the multiple marrow tumours in this disease may lead to its confusion with a generalized disease of bones. Such was the case when Bence Jones (1848) made his classic observations 'On a new substance occurring in the Urine of a patient with Mollities Ossium'.

He made a careful autopsy upon his case and regarded it, as the title implies, as a case of osteomalacia. Von Rustizky (1873) was the first to describe 'multiples myelom', a condition which he regarded as a simple hypertrophy of bone marrow. In 1889 Kahler was able to correlate the above observations and to show that Bence Jones had discovered a protein in the urine of a patient who had suffered, not from osteomalacia, but from multiple myelomatosis, as indeed his own careful protocol revealed (Macintyre, 1850).

Metastatic calcification, while by no means constant in this condition, has been frequently observed. Permin (1907) and Froboese (1916) have shown deposits of calcium salts in the kidneys. Austin (1911) found them in the lungs, Froboese in the uterine mucosa, and Tschistowitsch and Kolessnikoff (1909) in the myocardium. Taking into account the bone destruction, which occurs as a result of erosion by the marrow tumours, and also the metastatic calcification, it is not surprising that high serum calcium values have sometimes been found in this disease. In the case recorded by Charlton (1927) it varied from 12 to 16 mg. per 100 c.c., in that by Durman (1928) it was 16·1 mg. per 100 c.c., and in two further cases observed by Barr and Bulger (1930) it was 13·4 and 16·0 mg. per 100 c.c. Blatherwick (1916) and Currie (1927) each described a case showing an increased output of calcium in the urine.

Case of Haematogenous Myelomatosis with Parathyroid Hyperfunction (Bulger, Dixon, and Barr, 1930): A married woman of 46 years was admitted to hospital complaining of weakness, loss of weight, and pain in the back. The symptoms had gradually increased during two years. Examination showed emaciation and slight pallor of the mucous membranes. There was pain in the lumbar region and right shoulder, and dull aching pains shooting down the legs from the knees to the ankles. No Bence Jones protein was ever found in the urine, though albumin and casts were abundant. Red blood cells, 3,250,000. Haemoglobin, 48 per cent. White blood cells, 6,800. Non-protein nitrogen 38 mg., rising later to 70 mg. per 100 c.c. Radiograms of the bones showed pin-point rarefaction throughout all the lumbar vertebrae, ribs, and to a less extent in the pelvis. Serum calcium 15·4 mg., rising to 17·8 mg. per 100 c.c. Serum phosphorus 2·6 mg., rising to 5·3 mg. and later to 8·6 mg. per 100 c.c. On a calcium intake of 0·5 grm. daily there was a negative calcium balance. Six months after admission to hospital she died of broncho-pneumonia. At autopsy the bodies of the vertebrae, ribs, and clavicles were soft and cut easily with a chisel. Histologically the marrow in these bones was crowded with typical plasma cells. Metastatic calcification was found in the lungs, gastric mucosa, and kidneys. There were chronic degenerative changes in the kidneys with fibrosis of glomeruli and scarring of tubules. The thyroid was not enlarged; on its posterior surface there were several large smooth bodies lighter in colour than the thyroid tissue. Of six of these which were removed, three were found to be parathyroid glands; the largest measured 1·1 by 0·5 cm.

The important point in differential diagnosis in this case is that the high serum calcium is associated with a high phosphorus, whereas the characteristic effect produced by parathyroid hyper-function is a high serum calcium with a *low* phosphorus. Nevertheless, with the evidence at hand, it is logical to assume that in certain cases of haematogenous myelomatosis hyper-parathyroidism exists as a complication. Further, where this condition coincides

with renal insufficiency, the plasma phosphorus is found to be high and may rise as the kidney condition becomes worse. It should, however, be pointed out that reliable records exist of cases of haematogenous myelomatosis where the calcium and phosphorus metabolism was in all respects normal, and where normal parathyroids were found at autopsy.

The relation of bone destruction to parathyroid hyperplasia is evidently not a simple one. Klemperer (1923) has recorded a case of a parathyroid tumour associated with secondary carcinomatosis of bones. Here, as in the case of haematogenous myelomatosis quoted above, the skeletal decalcification seems to be a primary factor and the parathyroid tumour secondary.

Effects on Calcium Metabolism of Thyroxin and Thyroid Disease.

It is, of course, known that the internal secretion of the thyroid gland raises the basal rate of combustion of carbohydrate, fat, and possibly protein, consequently appreciably increasing the total heat production of the organism. Its effect, however, on inorganic salt metabolism had until recent years largely been ignored. Parhon (1912) showed a marked loss of calcium in rabbits fed with lethal doses of thyroid, and her work definitely suggests a stimulating effect of the thyroid on calcium metabolism. Kummer (1917) studied for thirteen days the metabolism of a man aged 42 suffering from exophthalmic goitre. Two and a half litres of milk were given daily, which meant that the calcium intake was approximately 5 grm. per day. No determinations were made of the basal metabolic rate, and control figures for calcium were taken from the literature. Because the quantity of calcium in the urine was normal, and that in the faeces was large, he attributed the high faecal calcium to a difficulty in absorption rather than to abnormal excretion. He concluded that the mineral excretion was high but very irregular, both the calcium and phosphorus losses being especially great.

It is to Aub, Bauer, Heath, and Ropes (1929), however, that we owe an accurate knowledge of the part played by the thyroid in calcium metabolism. Working with low calcium diets they have found that hyper-parathyroidism is associated with a markedly increased calcium excretion, and that the mechanism by which this is brought about differs widely from that of the parathyroid. They made observations on sixteen cases of thyroid disease, and on two normal individuals given thyroid, and in all these cases they found consistent results. In eight cases of exophthalmic goitre the elimination of calcium was 231 per cent. above the average excretion per kilo found in control cases. In one severe case of exophthalmic goitre the calcium excretion was eight times the normal. These increases were out of all proportion to the effect on the basal metabolic rate, the average increase of which was only 55 per cent. above normal. During treatment with iodine, and after subtotal thyroidectomy, as the patient improved and the basal metabolic rate approached the normal, the calcium excretion also returned towards normal.

Additional evidence was furnished by two cases of so-called hyperfunctioning adenoma of the thyroid. The calcium excretion was raised to almost twice the normal and fell definitely after the adenomata were removed. The effect of the administration of thyroid was studied in two normal individuals. In one of these 42 grains of thyroid extract were given by mouth over a period of four days, and on the fourth day 10 mg. thyroxin were given intravenously. Ten days later apprehension, fever, malaise, and tachycardia appeared. At this point the basal metabolic rate had risen to plus 48 per cent., and the calcium excretion was doubled. These studies clearly show that the thyroid hormone stimulated calcium excretion to an extent far in excess of that produced by acids, or even by parathormone. But if thyroxin increases calcium excretion, then myxoedema may be expected to be associated with a diminished calcium output. This was clearly established by these authors in six cases, where they found the average excretion to be 40 per cent. below the normal. Administration of thyroid to these patients with myxoedema resulted in an increase both in metabolism and in calcium excretion.

Thyroid treatment of parathyroid tetany. Striking effects were obtained by the use of thyroid preparations in a case of post-operative tetany (Aub, 1928). Sufficient thyroid extract by mouth and thyroxin intravenously were given to raise the basal metabolic rate from minus 14 to plus 22 per cent. This occurred over a period of two weeks, during which time the blood calcium rose from 6·7 to 11·9 mg. per 100 c.c. The calcium excretion increased to threefold its previous value. This increase of calcium in the blood and excreta was still present six weeks after the last dose of thyroid extract, a surprising result which was confirmed later in the same patient. This effect on calcium is not an indirect result of the raised metabolic rate, for the increased calcium excretion reached its height only when the basal metabolism was falling, and this increase was maintained long after the effect on the basal metabolism had subsided. This calcium stimulation, therefore, had a longer latent period and more prolonged effect than any other function of the thyroid yet described.

The effect of thyroid on the blood in this case is quite astonishing, when we recall that the serum calcium values in thyroid disease are normal. In exophthalmic goitre, even though calcium excretion may be eight times the normal, this high rate of elimination is not obvious in the blood, for there is no hypercalcaemia. And yet thyroid treatment has been found to raise the serum calcium in parathyroid tetany !

Action of thyroid and parathyroid contrasted. As to further contrasts between the thyroid and parathyroid mechanism Aub found that, of all the conditions he studied, it was in hyperthyroidism alone that he found a distinct increase in faecal as well as in urinary calcium excretion. It was also obvious that the faecal calcium was not unabsorbed calcium, for there was more present in the faeces than was present in the food. Why the faecal excretion should be increased above this basal level only by the thyroid is very difficult to understand, particularly as the blood calcium in thyroid disease is normal.

In hyperthyroidism a marked increase in phosphorus excretion was also found. This increase was quantitatively such as to suggest that most of the calcium excreted came from tertiary calcium phosphate in bone.

Is the high calcium excretion of hyperthyroidism dependent on the increased thyroid secretion, or is it merely an accompaniment of an increased metabolism? This question was answered by determining the calcium excretion in cases with a high metabolism due to prolonged fever and leukaemia. Three out of four such cases showed a normal calcium excretion in spite of an elevation of general metabolism, varying from plus 21 to plus 41 per cent. (Aub, Bauer, Heath, and Ropes, 1929). We may therefore conclude that an increased calcium excretion is not necessarily a function of a raised metabolic rate alone.

Does thyroxin exert a stimulating effect on the parathyroid glands? The normal blood calcium in hyperthyroidism and after intravenous thyroxin argues against this. But very little is known about the threshold of calcium excretion, and the administration of parathormone may sometimes cause a great increase of calcium excretion without appreciably raising the serum calcium level. The alternative explanation—namely, that the thyroid exerts a direct effect on bone katabolism—is not an unlikely one, especially as this would be in agreement with the general action of thyroid on other body tissues.

Radiographic studies of bones in exophthalmic goitre. The studies of Kummer (1917) on the metabolism in exophthalmic goitre led him to the conclusion that the calcium excretion was high in this disease. He was apparently the first to make the exceedingly interesting observation that 'as judged from radiograms this calcareous demineralization affects the bony system'. In 1927 Bernhard, investigating a case of exophthalmic goitre in a woman of 47, described radiograms showing poverty of calcium in the bones.

Aub, Bauer, Heath, and Ropes (1929) observed independently the same phenomenon. They took controlled radiograms of the hands of a patient with exophthalmic goitre of seventeen years' duration and demonstrated marked poverty of calcium in the bones. In their paper they point out that the change is unlikely to be a constant finding in hyperthyroidism, since adequate calcification of the bones should be possible in cases where the diet contains sufficient calcium.

Plummer and Dunlap (1928) found radiographic evidence of severe osteoporosis in three cases of hyperthyroidism, in two of which carcinomatosis of the bones had been suspected. An autopsy on one of these cases revealed generalized osteoporosis, especially of the calvaria and ribs, the latter showing multiple fractures. No histology is recorded. These authors state their belief that the process of decalcification of bone in hyperthyroidism is usual.

Hunter (1930) found that controlled radiograms of the bones in exophthalmic goitre revealed poverty of calcium in less than half the cases examined. In two cases of hyperthyroidism with spontaneous fracture there was radiographic evidence of decalcification, not only of the fractured bone but also of all other bones examined. The demineralization of bone seen in radiograms is, in fact,

a widespread osteoporosis brought about by osteoclastic lacunar resorption (Turnbull, 1930). It has already been emphasized that the serum calcium and plasma inorganic phosphorus are consistently normal in hyperthyroidism. The phosphatase values in the plasma are often high (Kay, 1930), though the increase is neither so great nor so consistently present as in the case of osteitis deformans. There seems to be no relation between the duration of the disease, the degree of osteoporosis, and the values for the plasma phosphatase (Hunter, 1930).

Osteoporosis in exophthalmic goitre. A search of the literature reveals the fact that osteoporosis occurring in thyroid disease was known to von Recklinghausen (1891). He described the case of a single woman of 23 with five years' history of goitre, prominence of the eyes, and palpitation. She complained of pain in the back over a period of two years, and later of pains in both arms. At necropsy there was great enlargement of the thyroid and thymus, with hypertrophy of the heart. Several of the bones were marked by uncommon redness for that age, especially the cortices of the long bones, which were everywhere marked longitudinally with vascular striae. Section of the long bones by sawing gave the impression of rotten wood, the sternum and calvaria being readily cut with a knife. Histologically, resorption spaces were abundant in the corticalis, and they often contained whole nests of osteoclasts. This author states that the degree of osteoclastic resorption was equalled only by that found in generalized osteitis fibrosa. He regarded the bone changes as secondary to the exophthalmic goitre, but expressed a doubt as to whether this form of 'osteomalacia' was identical with the ordinary puerperal form.

Askanazy (1901) confirmed this observation in a further case and stated that he had rarely observed in so dramatic and extensive a way the pure uncomplicated process of progressive bone resorption by osteoclasts. Reporting on the femur of a girl of 19 years of age who had died after an operation for exophthalmic goitre, Turnbull (1930) stated as follows: 'The compact tissue of the corticalis has been greatly rarefied by osteoclastic lacunar resorption; there is no histological evidence of a cessation of calcification such as is found in rickets and osteomalacia nor of a removal of calcium by chemical solution. This resorption is not confined to the corticalis, but is apparently greater throughout the spongiosa and medullary cavity.'

Irradiated Ergosterol.

Studies of calcium absorption and utilization are necessarily more difficult than those of endogenous calcium metabolism. It is not surprising, therefore, that the voluminous literature on the subject of irradiated ergosterol throws little light upon its mode of action. Hess and Lewis (1928) and others have reported hypercalcaemia arising from its use. But the level of the serum calcium indicates only the height of the 'calcium stream' and gives no indica-

tion of its direction of flow. This can be determined only by studies of the total calcium metabolism.

The effect of irradiated ergosterol on the storage of calcium in animals has been studied by Bauer and Marble (1929). They placed twelve cats on a low calcium diet for some months, previous experiments having shown that such treatment causes a marked diminution of bone trabeculae. At the end of this period the left forelegs of all the cats were amputated at the shoulder-joint. All twelve cats were then placed on a high calcium diet, six of the twelve being given irradiated ergosterol in addition. After some time the cats were killed, and in each case the right humerus was prepared for comparison with the left. The cats receiving irradiated ergosterol showed a much greater increase in the number of trabeculae in the right humerus than did the controls.

It therefore seems likely that irradiated ergosterol increases the amount of calcium which is absorbed from the gastro-intestinal tract, and that if this increased absorption occurs at a time when the body needs calcium, an increased deposition of calcium occurs in the bones. Complete metabolism studies on human subjects show that there is an increase in calcium absorption when irradiated ergosterol is administered (Bauer and Marble). These findings corroborate those obtained with cats and explain why the use of irradiated ergosterol in the treatment of rickets and osteomalacia has met with such uniformly beneficial results.

Effects of over-dosage with irradiated ergosterol. Considerable interest has recently centred on the effects produced by the administration of excessive doses of irradiated ergosterol. Pfannenstiel (1928) found that such doses resulted in the death of young rabbits. Kreitmair and Moll (1928) extended this work, and found that mice, rats, cats, rabbits, dogs, and guinea-pigs died in periods ranging from fifteen to forty days with doses varying from 1 to 40 mg. daily. In all cases the animals lost weight profoundly, and post-mortem examination showed deposits of calcium salts in the arteries, lungs, kidneys, stomach, and intercostal muscles. Kreitmair and Hintzelmann (1928) have since confirmed this, and they have added the important observation that, when the experiments are of long duration, there is a decalcification of the bones which especially affects the ribs but also involves the extremities, spine, and calvaria. Baumgartner, King, and Page (1929) confirmed this mobilization of calcium from the bones in 'hypervitaminosis D', and György (1930) has recorded experiments which seem to show that the spongiosa of bone is called upon first. In these experiments growing rats on a diet not very rich in calcium were treated with large doses of irradiated ergosterol. Hypercalcaemia occurred, and they lost appetite, weight, and hair. Post-mortem examination revealed macroscopic areas of calcification in the aorta and stones in the bladder. Controlled radiograms of the bones showed localized osteoporosis of the subepiphyseal spongiosa.

The method of irradiation of ergosterol. The work of Dixon and Hoyle (1928) has shown that the pathological changes produced in such experiments

on animals depend largely upon the manner in which the ergosterol is irradiated. In the case of material irradiated in oily solution—analogous to the natural irradiation of the ergosterol of the skin by sunlight—no abnormal effects upon the weight curve and no post-mortem lesions were found in rats after daily administration of doses up to 2 mg. for forty-five days. Much larger doses administered daily for a corresponding period led to interference with growth and the formation of calcium phosphate calculi in the urinary tract. Calcium deposits in the kidneys, arteries, and other tissues were not present in these animals. Dixon and Hoyle pointed out that the possible significance of these observations is not without interest in the aetiology of tropical urolithiasis.

The pathological effects produced in animals by administering similar doses of ergosterol irradiated in alcoholic solution are very much more severe than those described for material irradiated in oil. They consist essentially of intense marasmus and widespread calcification of the arterial system, myocardium, and kidney. Urinary calculi occur only rarely. Hoyle (1930) has shown that the diet given in such experiments is a determining factor in the production of this pathological picture. All the lesions occur constantly in rats when a synthetic diet is being taken together with a daily dose of about 80,000 antirachitic units of irradiated ergosterol, and death is usual within two or three weeks. If a natural diet of bread and milk is given, together with these excessive amounts of ergosterol irradiated in alcohol, the animals remain well, except for some retardation of growth. After thirty or forty days post-mortem examination in such animals shows urinary calculi in some cases but no calcium deposits in any of the organs. These latter effects are identical with those produced by giving similar doses of ergosterol irradiated in oil, together with a synthetic diet. In other words, the effect of a natural diet is to deprive ergosterol irradiated in alcoholic solution of certain toxic properties. This is strong evidence against the view that vitamin D and the toxic factor responsible for the marasmus and calcification of tissues are identical, and it shows that 'hypervitaminosis', as distinct from the toxic action, is not an entirely new type of toxaemia but only the exaggeration of a physiological action.

Hoyle (1930) found that over-irradiation of ergosterol in alcoholic solution, in order to destroy the antirachitic activity, had no effect in lessening its highly toxic properties. Marasmus, arterial degeneration, and calcification were produced quite as readily by such material as by actively antirachitic preparations, provided a synthetic diet was given during the experiments. This proves that such toxic effects must be due to some by-product formed during the irradiation of ergosterol and not to the antirachitic substance, vitamin D. Hoyle pointed out that it might have been anticipated that optimum antirachitic ergosterol would be more effective than over-irradiated ergosterol in producing calcification in the degenerative lesions which occur; but his experiments provided no evidence that this is the case. Clearly any part played by vitamin D in contributing to such toxic effects is of minor importance.

In further investigations it was found that neither milk nor bread alone,

when given with a synthetic diet, has any protective action against the toxic effects of alcohol-irradiated ergosterol. Further, a synthetic diet modified to resemble bread and milk as regards its carbohydrate, fat, and ash content does not prevent the toxic action of ergosterol irradiated in alcoholic solution. If the amount of the latter in a diet be increased still more, to such doses as 200,000 units daily, then bread and milk loses its protective effect. These results suggest that some previously unrecognized factor in diet is concerned in the protective action.

Rickets.

What we know of the pathogenesis of rickets we owe to studies of experimental rickets. E. Mellanby worked with puppies, doing almost 400 experiments, the accounts of which he published in 1918 and 1919. The puppies developed rickets on diets deficient in calcium and fats. In some of them he succeeded in curing the rickets by giving cod-liver oil, or, less effectively, by butter fat or suet. In others he failed entirely to cure it by lard, or by cotton seed, olive, or linseed oil. The fats which he found richest in antirachitic power, cod-liver oil and butter, were also those which, five years earlier, had been shown to be richest in vitamin A. In 1921 McCollum and his co-workers developed methods which enabled them to produce rickets in rats in a short period. They were able to show that the antirachitic factor in cod-liver oil is distinct from vitamin A. Realizing that this vitamin is readily oxidized they passed a stream of oxygen through heated cod-liver oil and used the product in feeding experiments. It no longer cured xerophthalmia in rats, but it retained its antirachitic effect (McCollum, 1922). The new vitamin was ultimately called vitamin D.

They also turned their attention to the calcium and phosphorus content of both the food and the blood, and found that as long as the ratio of calcium to phosphorus in the food is kept at an optimum level rickets does not develop, even in the complete absence of antirachitic substances from the diet. But should there be a marked relative increase or decrease of the same ratio, together with a deficiency of vitamin D, then rickets develops. In this way they created two forms of experimental rickets, the one developing on a diet poor in phosphorus and histologically identical with the common form of rickets in children, the other developing on a diet poor in calcium and histologically showing osteoporosis in addition. Similarly, the blood chemistry of the two groups of experimental rickets was found to correspond to that in children, the plasma phosphorus being more commonly reduced than the serum calcium (Howland and Kramer, 1921). In human rickets the plasma phosphatase is high (Kay, 1930).

Healing is almost invariably accompanied by a return of the blood chemistry towards normal. Zucker and Matzner (1924) claimed that healing was accompanied by a change of the reaction of the stools from alkaline to acid, and that the change was pathognomonic. Shohl and Bing (1928), however, have shown that this is not constant. That starvation may lead to the healing

of rickets has been observed both experimentally and clinically. It occurs only in the low phosphorus type of the disease. It is possibly an effect produced by phosphorus liberated from organic combination during increased endogenous metabolism.

In addition to the above considerations E. Mellanby (1925) has discovered that cereals, and especially oatmeal, have a specific rachitogenic effect. The substance concerned, so-called toxamin, is not indispensable for the development of rickets. This work, which was carried out on low-calcium rickets in dogs, has been confirmed in rats suffering from low-phosphorus rickets (György, 1929).

The antirachitic power of ultra-violet irradiation was discovered in 1919 by Huldschinsky. In children suffering from severe rickets he demonstrated by radiograms the healing effects of the mercury vapour quartz lamp and of sunlight. In 1924 it was discovered that certain foods developed antirachitic powers by exposure to ultra-violet irradiation (Hess and Weinstock). It has since been possible to cure rickets in children by feeding them on irradiated foods. It is the sterols in such foods that can take on antirachitic potency, in particular ergosterol, for vitamin D is a derivative of this substance, or of some closely related sterol (Rosenheim and Webster, 1927). In the case of the skin the antirachitic action of ultra-violet irradiation is probably due to the synthesis of vitamin D from the ergosterol which it contains.

Osteomalacia.

Morbid anatomists are agreed that in rickets and osteomalacia the essential abnormality is the same, namely, a deficient calcification of osteoid tissue. This deficiency is generalized throughout the skeleton. In rickets, since endochondral ossification has not ceased, the zone of provisional calcification is affected too, and endochondral ossification is irregular.

The nature of the calcium deficiency has given rise to much controversy. Virchow (1853) held the view that calcium salts had been removed from calcified bone leaving osteoid tissue. This was the doctrine of 'halisteresis', which means literally 'salt deprivation'. Pommer (1885) and Schmorl (1909), while expressing the view that osteomalacia and rickets are essentially the same disease, held in addition that halisteresis is not responsible for the broad osteoid zones. They considered that, in both diseases, the calcifying mechanism which should convert osteoid tissue into true bone was deficient. Not only does any bone added by advancing endochondral ossification remain osteoid, but so also does all new bone added to trabeculae which were fully calcified at the onset of the disease. The normal physiological resorption accompanies this apposition, and consequently portions previously hard become ever softer and more liable to bend.

Now, although there are many problems still unsolved concerning the aetiology of these two diseases, it is clear that the calcifying substance which

is missing is vitamin D. In its absence the utilization of calcium and phosphorus is impaired. In the majority of cases of osteomalacia the serum calcium is low as in low-calcium rickets. In both diseases the abnormalities in the blood are promptly restored to normal by the use of cod-liver oil, ultra-violet light, or irradiated ergosterol. At the same time ossification begins to proceed normally. Biochemistry has therefore amply justified the view held by Pommer and Schmorl of the pathogenesis of these diseases and their essential identity.

Clinical features of osteomalacia. Osteomalacia is a deficiency disease endemic over wide areas in Northern India, Japan, and Northern China, and occurring sporadically in the Rhine Valley, Danube Valley, Vienna, and certain parts of Italy, Switzerland, Flanders, and the Balkans. It is a rare disease in the British Isles and U.S.A. It pre-eminently affects women, and is likely to recur earlier and with greater severity in each successive pregnancy. Many cases clear up after lactation is complete, or even before this time. However, it is a mistake to suppose that pregnancy is essential in its aetiology; it is sometimes seen at puberty, and is quite well known to occur, though it is rare, in boys and men (Wilson, 1931). Maxwell (1923) states that it is known to the Chinese as 'Yao t'ui t'eng'—'back and thigh pain'. The pain is aching in character and is worse in the winter months. The pelvis, thorax, or long bones show deformity in a haphazard way; one woman suffers in the pelvis, another in the ribs, and a third in both. Besides the characteristic and well-known change in the pelvis, marked deformities occur in the chest and spine. Severe kypho-scoliosis may reduce the height by several inches and cause the head and neck to sink downwards and forwards on to the chest. Deformities of the sternum and ribs may give rise to marked prominences and depressions in the chest wall. Coxa vara and irregular curves in the long bones are less common. The bones are soft and flexible rather than fragile, so that bending is much more common than spontaneous fracture, though both are well recognized. The patient develops a characteristic waddling gait, and muscular weakness may add to her incapacity. In many cases the pelvic deformities interfere with marital relations or with pregnancy, Caesarean section frequently being necessary. Tetany is very common, and the attacks may last for hours. Wilson (1931) has found evidence of osteomalacia in cases of the so-called idiopathic tetany or 'wai' of Kashmir.

Pathogenesis of osteomalacia. It is only in recent years that real progress has been made towards solving the problem of the aetiology of osteomalacia. For almost half a century the hypothesis was held that the disease was due to a pathological increase in the activity of the ovaries leading to hyperaemia of the bones and a consequent solution of their lime salts. This was not based on accurate experiment, neither was there any evidence worth the name that the ovaries were histologically abnormal. The hypothesis arose in 1879 when Fochier performed Caesarean hysterectomy in several cases of osteomalacia and found that a good effect was produced on the progress of the disease. Fehling (1884) performed ovariotomy for osteomalacia quite apart from pregnancy, and

within a few years this treatment was performed all over the world. Now, while there can be no doubt that pregnancy leads to the development of osteomalacia, there is very little evidence that the ovaries exert any effect on the disease apart from their rôle in pregnancy. Castration presumably acts by stopping the possibility of further pregnancy and lactation with their consequent drain on skeletal calcium, and this can be as easily done by ligature of the Fallopian tubes.

An amazing fallacy regarding the aetiology of osteomalacia originated in the work of Bossi (1907), who arrived at a method for treating the disease with adrenalin by the following argument: 'Since suprarenal substance is known through its pressor action to modify deeply the circulation in both sexual organs and bone marrow, since removal of the suprarenal has been shown in animals to cause deep and lasting changes in the ovary, I thought of treating this case with suprarenal substance (adrenalin).' After claiming, on quite inadequate evidence, that the patient was cured by the injections, he proceeded to an experiment upon a sheep in the middle of pregnancy. He removed one suprarenal and the animal remained well until the seventh day, when it had difficulty in walking. On the eighth day it could neither stand nor walk, and it showed 'curvatures of the joints in the whole body, the hips markedly rotated inwards, and painful on pressure'. Such is the evidence on which the suprarenal origin of osteomalacia is based. One asks oneself whether its exponents of to-day have troubled to read the article from which it sprang!

Studies of the mineral metabolism of osteomalacia date back many years, and began with analyses of the bones. McCrudden (1910) in a case of adolescent osteomalacia found 15·4 per cent. CaO in dried bone as compared to 28·8 per cent. in normal bone. In 1910 the same observer demonstrated a negative calcium balance in eight cases of osteomalacia.

The blood chemistry had not been studied accurately until Miles and Feng (1925) investigated ten patients. These cases varied in duration from eight months to twenty years; in seven there was tetany, and in all a considerable diminution in the serum calcium (5·0 to 7·4 mg. per 100 c.c.). The plasma phosphorus varied from 1·8 to 3·8 mg. per 100 c.c. The same workers carried out calcium balance experiments on four adult females taking a low calcium diet consisting of millet gruel, wheat bread rolls, celery, cabbage, garlic, and dry steamed millet. A negative calcium balance was found in three patients, positive in one. Keeping the diet identical and adding cod-liver oil, alone or in combination with either calcium lactate or calcium phosphate, they were able to bring about marked retention. In one patient receiving olive oil with calcium lactate, the calcium balance remained negative. Osteomalacia therefore chemically resembles low calcium rickets. In the present state of our knowledge the occurrence of hyperplasia of the parathyroids in osteomalacia (Erdheim, 1907) is without explanation. Since all the parathyroids are usually affected, the hypothesis that the change is compensatory seems attractive.

Economic factors responsible for osteomalacia. With the story of rickets

before us we can trace the economic factors operating in the causation of osteomalacia. They are factors difficult for a Western civilization to appreciate, deep-rooted as they are in the social and religious customs of the East. The diet of the Chinese people is meagre, consisting, as in the experimental diet used by Miles and Feng, entirely of cereals and a limited amount of vegetables with no milk, meat, or eggs. It is deficient in vitamin D and in calcium salts, and contains an excess of acid-forming over base-forming mineral elements. The environment tends to keep the woman patient isolated from the sun, for foot-binding retards movement, and the severe winters of the high plateau lands of North China lead to confinement indoors. When the pains of osteomalacia begin she retires to her warm brick bed thereby completely shutting herself off from the sun. In India the areas affected are in the North, in the high valleys where sunlight is scanty in winter owing to the surrounding mountains. As in China there is a marked seasonal incidence, the disease being worse in winter and early spring. The women affected are those observing strict purdah (Vaughan, 1926). They are systematically screened from the sun from the age of ten. They eat no raw vegetable or fruit, largely from fear of cholera. The pregnant woman is kept short of food with the idea of keeping the foetus small for an easy labour. The calcium drain of lactation is very severe, for it commonly goes on as long as four years. Under such social systems it is not surprising that other deficiency diseases may exist together with osteomalacia. Thus Wampler (1924) reports oedema in one-third of forty-six cases, and xerophthalmia in one.

In the treatment of osteomalacia, as in the case of rickets, cod-liver oil, sunlight, and irradiated ergosterol, each has its place. Vaughan reports that 'out-patients given cod-liver oil and ordered to go out on the lake in open boats improved rapidly'. Starlinger (1927) and Hottinger (1927) report cures with irradiated ergosterol, and it is an interesting fact that each of their cases had been previously treated unsuccessfully by ovariotomy. Maxwell states that 'given cod-liver oil, good food, and sunlight, the majority of the patients will slowly recover. Cod-liver oil and calcium salts quickly remove tetany and the worst of the pain.' He finds that some cases require an ounce and a half of cod-liver oil with one milligram of irradiated ergosterol daily. But he adds, 'we want flocks and herds, milk and meat, with security of life and property'.

Antenatal Rickets.

In the days of Virchow, several diseases of bone discoverable in the new-born were classed together as 'foetal rickets'. These have since been identified as achondroplasia, osteogenesis imperfecta, and cretinism. Maxwell (1930) claims to have found true rickets in antenatal life. He took radiograms of the bones of the new-born babies of osteomalacic mothers, and demonstrated the typical changes of rickets in the metaphyses. Microscopic preparations of the bones were obtained from one case. In these, Turnbull found changes attributable

to a mixture of rickets or osteomalacia, with Barlow's disease. It is of some importance, too, that babies of osteomalacic mothers do get post-natal rickets, and that in China rickets is especially severe where osteomalacia is more common.

Influence of Diet on the Structure of Teeth.

The occurrence of hypoplasia of the teeth with defects both in the enamel and the dentine has been recognized for years in rickets. Such malformations are by no means exclusively of rickety origin, for they occur in other disturbances of metabolism. According to a number of authors a lack of vitamin C leads, in guinea-pigs, to defective teeth (Zilva and Wells, 1919). The changes here commence in the pulp, the dentine being affected later.

M. Mellanby (1928) has studied the teeth extensively in dogs and in children. On a diet deficient in vitamin D, particularly if it was rich in the so-called rachitogenic cereals as well, the dogs developed severe hypoplasia of the teeth, whereas the controls receiving antirachitic substances in addition had sound teeth. She showed that in children energetic administration of cod-liver oil or irradiated ergosterol lessened the incidence of such defective teeth and of the caries to which they are subject. Further, even in the presence of defective teeth, caries occurred far less readily in children so treated (Mellanby and Pattison, 1928). In two groups of school children, one group treated and the other not, the average incidence of caries was respectively 1·4 and 5·1. M. Mellanby showed that in dogs dental defects can occur in the first dentition as a result of a deficiency of vitamin D in the food of the mother. Walkhoff (1929) has demonstrated in guinea-pigs a similar effect in the case of vitamin C.

Hunger Osteopathy.

Occasional cases of hunger osteopathy were known before 1914 (Partsch, 1919), but the mass experiment of war caused large numbers of cases to appear in Austria, Germany, and Poland between 1917 and 1919. Concurrently rickets (Dalyell and Chick, 1921), late rickets, and osteomalacia (Hirsch, 1920), increased in incidence and severity. The people of industrial towns were most affected. Thus in Frankfort the food was principally potatoes, watery soups, and dried carrots. Fresh vegetables were rarely obtainable. Meat, fish, and bread were rationed. Fat, butter, cheese, eggs, milk, and rice were completely absent. Hence the diet was deficient not only in total calories, protein, and fat, but also in calcium, phosphorus, and vitamins.

Clinically, the condition resembled early and slowly progressing osteomalacia. In age and sex incidence it was most peculiar. The majority of patients were elderly, and of either sex. Adolescents between 14 and 20 years were also attacked, and in this age-period two to four times as many males were affected as females. Children from 6 to 14 years were absolutely spared, and people from 20 to 35 years were almost wholly immune. The poorest were

most affected. They looked prematurely aged, with sunken orbits and a sallow colour. Pain in the tarsus and metatarsus gave rise to difficulty in walking. Later there was pain in the sacrum and ribs, with a characteristic waddling gait and difficulty in mounting steps. The pains were always associated with movement. Many patients complained of cramps in feet, legs, or forearms. Tetany was not infrequent, and some cases showed positive Erb, Trousseau, and Chvostek signs (Schlesinger, 1919). There was tenderness of the bones, so that compression of the ribs and sacrum and abduction of the thigh caused pain. A few patients gave a definite history of decrease in height. Spontaneous fractures were sometimes seen (Eisler, 1919), and occasionally deformities of ribs, sternum, and spine (Partsch, Schlesinger).

Dalyell and Chick found a marked remission in the disease in Vienna in the late summer of 1919. In December, 1919, they found fresh and recurrent cases in two convents in which the nuns had suffered severely during the previous winter. Between January and May, 1920, they treated 600 outpatients with the disease. For obvious reasons no investigations of the blood chemistry could be made. Cod-liver oil was found to be a specific. After a few days movements of the trunk became less painful, so that the patient could stoop or turn readily. The gait often improved within a week. During the second week there was less pain on abduction of the hip, but pain caused by compression of the ribs continued longer. The most obstinate pains were the lumbo-sacral and tarsal, which sometimes persisted for six weeks after the commencement of treatment. In cases with tetany this improved before the other symptoms and signs. From what we now know of vitamin D, the remission of symptoms in summer and their relapse in winter was a question of the amount of sunlight; and from accounts of the disease it is evident that no therapeutic measure was successful unless it included vitamin D. Post-mortem material was only obtained where deaths occurred from intercurrent disease. There has been much controversy as to whether the condition was true osteomalacia, and this, of course, can only be settled by the expert histologist.

Schmorl (1920) and Partsch, working in Dresden, regard the condition as true osteomalacia showing an extreme degree of osteoporosis. They comment upon the rarefaction of the corticalis; in one case 'the compacta of the femur was nowhere more than 3 mm. thick'. In the vertebrae the corticalis was almost as thin as paper, and the spongiosa could be crushed with the finger. The histological picture showed the spicules of the spongiosa much reduced in number and in thickness, and composed of narrow cores of bone covered by broad seams of osteoid tissue.

Goldschmid (1926), working in Frankfort, states that 'purely porotic changes predominate in the bones, though there are quite isolated cases where thin spicules covered with narrow osteoid seams are found in the spongiosa—that is a combination of porosis with malacia'. The student of mineral metabolism would predict such disagreement between histologists since so many factors, varying in different localities, came into play. These variables were

degree and length of starvation, amount of calcium, phosphorus, vitamin D, and other vitamins in the diet, and exposure to sunlight. It is interesting that Schmorl (1920) should have found enlargement of the parathyroids in a man of 73 who had suffered from hunger osteomalacia with pains in the bones for three months. He states that 'there was a very great enlargement of the parathyroids, the two upper ones being the size of a cherry stone, and one lower one the size of a pea. The fourth was not found.'

Styfsiekte, or Stiff-sickness of Cattle.

Styfsiekte, or 'stiff-sickness', is a phosphorus deficiency disease of South African cattle. The problem of its aetiology has been solved by the extensive investigations of Sir Arnold Theiler (1924, 1927). The disease also occurs in Minnesota (Palmer and Eckles, 1926), and is probably identical with the 'Grand Traverse Disease' of Michigan, 'Impaction Paralysis', and the 'Cripples' of Australia, and 'Midland Disease' of Tasmania (Corlette, 1928). The animals most affected are heifers with a first calf, cows in lactation, and growing cattle. They may develop an intense craving for bones, a symptom which is termed osteophagia. This compels them to travel long distances to find carcasses to eat, and they may even kill and eat young lambs. On the veld they may sometimes be seen and heard in the distance crunching bones. The disease shows itself in retardation of growth and abnormal skeletal development, the most obvious features of which are the thickening of the epiphyses of the leg bones, most pronounced at the metacarpus and first phalangeal joints. The gait is stiff and lame. In the young lactating animal there is usually rapid loss of condition, the lameness may become acute, and the animal tends to walk on its heels with hoofs growing out. The bones may become fragile, and fracture of the ribs and pelvis has been observed. The posture becomes abnormal, sometimes with curved spine, and in the last stages the stiffness and lameness become so painful that the animal is unable to rise, so that death from cachexia ensues. In the affected areas the soil and grass are deficient in phosphorus, so that hay may contain less than one-fifth the normal amount of phosphorus. The blood chemistry has been investigated in the Minnesota cases. There the low phosphorus intake gives rise to a low inorganic phosphorus content of the plasma, which is often less than 2 mg. per 100 c.c. There is no defect, however, in the calcium content of the fodder, and the serum calcium of affected cattle is normal or even raised (12·1 to 14·6 mg. per 100 c.c.). The bones are fragile and easily cut with a knife, and the skeleton is light.

Theiler, Green, and du Toit (1927) have reproduced experimentally 'aphosphorosis', or clinically recognizable phosphorus deficiency disease, and have shown it to be identical with the naturally occurring South African disease Styfsiekte. The animals were heifers varying in age from twelve to eighteen months. All of them received exercise each day in brilliant sunshine. The disease picture was produced in all animals where low-phosphorus rations were

given, whether the calcium content of such rations was high or low. The inorganic phosphorus of the blood sometimes dropped to 1·3 mg. per 100 c.c., even before the disease could be diagnosed clinically; the blood calcium was normal. Vitamin deficiency of the diets had no adverse effect. Of the affected animals dying or killed some showed brittle, fragile, or fractured ribs, the whole of the skeleton being too light. Sir Arnold Theiler is at present working on the histology of experimental aphosphorosis, and he states that 'the sections reveal the presence of osteomalacia and rickets in some cases in a most extraordinary degree'.

Styfsiekte is, therefore, rickets or osteomalacia of the 'low phosphorus' type, produced by a mass experiment of nature in areas where the soil and grass are deficient in phosphorus. Sunlight is apparently unable to prevent its occurrence. As further evidence that the condition is one of pure phosphorus deficiency, the South African workers found that the disease can be prevented by supplementing the grazing of the areas in which it is prevalent with bran, which is a food of high phosphorus, low calcium content. Similarly, the Minnesota workers, by a supplementary ration of 100 grm. daily of NaH_2PO_4 were able to raise the plasma phosphorus to 5·5 mg. per 100 c.c. with complete clinical cure. The routine preventive is bone meal. The ration required varies from half a pound to two pounds per head per week, according to conditions of growth and lactation. This simple measure abolishes osteophagia and Styfsiekte, and leads to an increase of the milk yield of cows, better calves at birth, more rapid growth of young stock, and superior fattening of adult cattle.

Late Rickets.

Late rickets is found in the later years of childhood in places where rickets is common. It is also found where osteomalacia is endemic. Its pathogenesis, blood chemistry, and histology enable us to class it definitely with rickets and osteomalacia. With a knowledge of vitamin D, and especially of the newer methods of blood chemistry, two conditions associated with bone deformities have been differentiated from late rickets—namely, coeliac rickets, and renal rickets. It should be clearly understood that cases of coeliac disease and renal infantilism only occasionally show rickets; in fact, coeliac rickets is quite rare in coeliac disease.

Although these two conditions show clinical pictures quite different from rickets, the actual bone changes may be identical with that disease. This point is of paramount interest in the study of calcium and phosphorus metabolism, for in renal rickets vitamin D is not lacking, and the bone changes are due to a disturbance of endogenous and not of exogenous metabolism.

Coeliac rickets. Coeliac infantilism may be defined as the arrest of development which occurs in that form of severe chronic intestinal indigestion described by Gee (1888), and explained on the basis of defective fat absorption. In 1913, Parsons pointed out that bone deformities, especially genu valgum, not uncommonly complicate coeliac disease, and in 1927 he investigated the blood

chemistry in five such cases. The serum calcium was constantly low, and the plasma phosphorus occasionally low. Tetany was commonly present. In cases of moderate severity, the radiographic appearances of the bones were striking. They showed delay in the centres of ossification, osteoporosis, and conspicuous abnormalities in the metaphyses. Except that it was not so much splayed out, the metaphysis did not differ from that found in ordinary rickets. Single or multiple, complete or incomplete, fractures of the shaft were frequently observed. McCrudden and Fales (1912) related osteoporosis and fractures to the negative calcium balance which they found in the disease. Lehndorff and Mautner (1927) pointed out that a child with coeliac disease is liable to spontaneous fractures. Coeliac rickets can be completely cured, even when the patient is on a fat-free diet, by ultra-violet light or irradiated ergosterol (Parsons, 1927). It is, therefore, fair to say, even in the absence of histological records, that the combined evidence strongly favours a rachitic origin of the bony changes sometimes found in coeliac disease.

Idiopathic steatorrhoeas of adults. Since the description by Herter (1907) of intestinal infantilism, later authors have paid attention only to cases of steatorrhoea in children, and have forgotten that Gee also observed the condition in patients returning from India and in adults who had never been abroad. The occurrence of tetany is not uncommon in tropical sprue. It is associated with a low serum calcium, and is no doubt related to deficient calcium absorption. However, it has been found that even severe and cachectic cases of sprue often have a normal serum calcium (Ashford and Hernández, 1926). The cause of sprue is unknown, and whatever calcium defect may be found is of secondary importance only. Cases in adults of fatty diarrhoea with tetany, accompanied by extreme wasting, occur sporadically in temperate regions. Of these it is equally true that the cause of the defective absorption of fat is unknown, and that the defect of calcium absorption is of secondary importance only. Thaysen (1926) regards them as cases of non-tropical sprue, and includes them with sprue and with coeliac disease in the term 'idiopathic steatorrhoeas'. Cases have been recorded of patients who had coeliac disease in childhood and recurring diarrhoea and tetany in adult life.

The fat in the stools is mostly split fat. There is pallor and sometimes severe anaemia (Holmes and Starr, 1929). There is often clubbing of the fingers. The abdomen is distended, and the colon may be dilated. Bone deformities are common (Hunter, 1930), and include genu valgum, genu varum, bowing of femora and tibiae, and spontaneous fractures. Achlorhydria is common, and the blood-sugar tolerance curve may be low (Thaysen). The plasma phosphorus is greatly reduced, and the serum calcium may be low. Metabolism studies suggest that the chief factor concerned in the calcium defect is a failure to absorb vitamin D, and that the formation of calcium soaps is not an important factor in preventing calcium absorption (Linder and Harris, 1929). Treatment by fat restriction and irradiated ergosterol is sometimes effective.

Renal rickets. Albuminuria associated with deformities of the extremities

was noted by clinicians some fifty years ago, but the inter-dependence of disease of the kidney and of the bones was not suspected. Fletcher (1911) was the first to appreciate this, and in 1912 Miller and Parsons published an account of several cases. The credit for emphasizing the relationship between the renal disturbance and the bony deformities belongs to Barber, who, since 1931, has published a series of papers on the subject. In renal dwarfism the stunting of growth and delayed union of epiphyses often occurs without clinical or radiological evidence of rickets. It is equally certain that rickets occasionally complicates renal dwarfism. Where it does so all the histological characteristics of true rickets have been demonstrated. And yet this condition is not due to lack of vitamin D, but to a disturbance of endogenous calcium and phosphorus metabolism for which the chronic nephritis is evidently responsible. Late in the disease the plasma inorganic phosphorus rises with the rise of blood urea (Parsons, 1927). The serum calcium tends to fall as the plasma phosphorus rises, hence the high incidence of tetany in this disease. The plasma phosphatase is high (Kay, 1930). The theory that phosphate retention, due to the renal defect, is primarily responsible for the changes in the bones is clearly unsatisfactory.

Osteitis Deformans.

In the original description of the disease which bears his name, Paget (1877) apologized for the use of the term 'osteitis deformans' as obviously inadequate. By analogy with generalized osteitis fibrosa it seems likely that Paget's disease is a disorder of mineral metabolism. According to Turnbull there is only one definite histological difference between the two diseases, but it is a big difference. In osteitis deformans (Paget) there is tremendous resorption of bone associated with tremendous apposition completely altering the normal architecture, but apposition preponderates. In generalized osteitis fibrosa (von Recklinghausen) widespread resorption of bone is the essential change, and excessive apposition is focal and relatively insignificant. Enlargement of the parathyroids has apparently not been demonstrated in Paget's disease, but the use by German authors of the term 'osteodystrophia fibrosa' to include many generalized diseases of bones makes this question unduly involved.

In Paget's disease the serum calcium and plasma phosphorus are approximately normal. Such studies as have been made of the calcium balance have given conflicting results, but no departure from the normal of any magnitude has been demonstrated. The discovery by Kay (1929) that the plasma phosphatase is constantly high in this disease is of great interest. He points out (1930) that the value may rise in some cases to more than twenty times the normal average value. His cases of osteitis deformans represent all stages of the disease, from those in which apparently only one bone was involved to those in which almost every bone in the body was affected. There is a rough correlation between the severity of the disease and the level of the plasma phosphatase. The most severe cases all had very high values; the milder cases usually, but

not invariably, had less high values. Kay (1930) points out that this may be because there is relatively little excretion of the enzyme from the circulating blood. In the urine of four cases he found no increased excretion of phosphatase. A high plasma phosphatase level, therefore, may not necessarily mean a continuous high rate of leakage of phosphatase from the bones into the bloodstream, but a chronic slow diffusion thither at slightly above normal rates.

It is important to remember that though Kay's work affords us a valuable aid in diagnosis the test is not pathognomonic, since high plasma phosphatase values are also found in generalized osteitis fibrosa, secondary carcinomatosis of bones, and in some cases of exophthalmic goitre.

Osteogenesis Imperfecta.

This condition was first clearly defined by Lobstein (1833) who gave it the name osteopsathyrosis idiopathica. In 1849 Vrolik described the pre-natal type of the disease in which multiple fractures occur *in utero* and the child is often born dead. In both types the basic defect appears, from histological examinations, to be an inability to form osteoblasts. These are commonly described as few in number and anomalous in structure, that is to say, there is a failure on the part of certain primitive cells to differentiate into their normal tissues. In considering the chief clinical manifestation of the condition it must be remembered that the degree of liability to fracture from inadequate causes varies in different individuals and usually tends to become less after puberty. Persons affected tend to be short in stature and slender in build. As a result of anomalous cranial ossification the shape of the head is often a striking feature. A bi-temporal protuberance, so marked as to turn the ears outward in some cases, is frequently described, but protuberances of the occipital region, and again of the frontal regions, are common features. In extreme cases, and especially in the pre-natal type, the cranial ossification is so disorganized that the resulting vault of the skull may consist of a mosaic of small Wormian bones. Three other defects commonly occur in association with the fragile bones, namely, blue sclerotics (Eddowes, 1900), a tendency to dislocation of joints, and, after the age of 20 years, otosclerosis. Regarding the inheritance of blue sclerotics, Bell (1928) has shown that the female is especially liable. She found that amongst the adult population affected with blue sclerotics approximately 60 per cent. of members have an associated liability to fracture, approximately 60 per cent. of members have an associated otosclerosis, and 44 per cent. of members suffer from all three defects. Osteogenesis imperfecta sometimes occurs in an hereditary form without blue sclerotics.

No abnormality in the serum calcium, plasma phosphorus, or calcium output has been satisfactorily demonstrated. The plasma phosphatase tends to show a raised value, but this is not constant. Kay (1930) examined six cases and found that the highest values occurred in the youngest patients. The

average for four children was 0·50 mg.; the normal value for their age, namely 7 years, is in the neighbourhood of 0·22 mg. There are two cases recorded which showed enlargement of the parathyroids. The seven-months foetus described by Bauer (1920) had four enlarged parathyroids, the largest the size of the adult gland (3 mm. diameter). Histologically these showed hyperplasia. He relates that Dietrich (1915) described another case. In the present state of our knowledge such observations are without explanation.

Otosclerosis.

Otosclerosis was first recognized as an entity by Toynbee in 1841. It is largely hereditary, and occurs most frequently in females in whom its onset is associated with puberty, pregnancy, or lactation; it is progressive, but is usually arrested at the menopause. The deafness is often bilateral, and is due to changes in the compact bony capsule surrounding the labyrinth. Certain characteristics in its pathology suggest that it may be due to disturbances in metabolism. Amongst these is its association with generalized diseases of bones. It is commonly found in osteogenesis imperfecta after the age of 20 years, it sometimes occurs in osteitis deformans (Paget), whereas it is seen only rarely in generalized osteitis fibrosa (von Recklinghausen). Leicher (1928) claims that the serum calcium is often low, and the occurrence of latent tetany becoming manifest during pregnancy has been pointed out by Frey and Orzechowski (1920). Bauer and Stein (1924) found latent tetany and genital hypoplasia to occur frequently in otosclerosis. In a series of cases of otosclerosis Aub (1928) showed that the serum calcium and calcium balance were normal. He failed to cause improvement in the acuity of hearing by injections of parathormone, although many grammes of calcium were eliminated from the body. Mirvish (1930) treated three cases in the same way, and claims that in two of the cases there was considerable improvement in hearing, and that in the third the progress of the deafness was arrested. These conflicting observations merely emphasize our complete ignorance of the real nature of this disease.

Storage and Excretion of Lead.

Studies of lead poisoning have revealed a close analogy between the storage and excretion of lead and of calcium. Since lead is a cumulative poison there must be some place in the body where it can be retained in fairly large quantities. The work of Gusserow (1861), followed by that of Heubel (1871), showed that this storehouse was the skeleton. Minot and Aub (1924) demonstrated quantitatively in animals and man a selective localization of lead in the bones which becomes practically complete after absorption has ceased. Fairhall (1924) studied such bones, and the results of his experiments suggest that the lead is present as the very insoluble tertiary phosphate. Various experiments showed that this is deposited in the calcareous portion of the bone, and not in the marrow.

During different stages of intoxication by lead its distribution within the body varies somewhat. During slow absorption it migrates to the storehouse in the skeleton, where about 95 per cent. is held without harm during the chronic stages of plumbism. However, if large quantities of lead are being absorbed or are being liberated from the bones, lead is distributed throughout the tissues and the percentage in the bones is reduced. Under these conditions symptoms of acute poisoning may occur. Working with human autopsy material, Minot and Aub have shown that the total amount of lead stored in the skeleton in lead workers varies from 0·2 to 0·8 grm.

Lead stored in the bones may be gradually excreted in minute amounts over long periods. It has been found in the stools of persons who have been removed from exposure for more than two years, and Sir Thomas Oliver reports finding it in the urine of a woman eleven years after exposure. Thus, as suggested by Straub (1911) and by Erlenmeyer (1913), there may be an intermittent stream of lead entering the circulation to be excreted gradually.

Effect of ammonium chloride on elimination of lead. Aub and Minot studied the conditions favouring and hindering liberation of lead from the bones in cats experimentally poisoned with lead. Early in their investigations they found that during starvation acute symptoms may develop, and at necropsy lead is found distributed more generally through the body than is typical of the chronic condition. This suggested that during starvation there is some abnormality in metabolism which sets free lead from the bones. Acidosis seemed the most probable explanation for the change, and an investigation based on this hypothesis was undertaken.

Lead workers were placed on a low calcium diet, and were given either hydrochloric acid, phosphoric acid, or ammonium chloride in large doses. The excretion of lead in the faeces was markedly increased. The probable reason for the increased liberation of lead during acidosis is to be found in the experiments of Fairhall. He studied the effect of variations in the hydrogen-ion concentration upon absorption of lead by bone. The tertiary phosphate of lead has an extremely low solubility at the normal pH of the body. However, under slightly more acid conditions, it is readily converted into the secondary phosphate of lead ($PbHPO_4$), which is a hundred times more soluble. Hence the ingestion of acid probably served to liberate lead from the skeletal stores by converting it into a more soluble salt.

Effect of parathyroid extract in lead poisoning. When active parathyroid extracts became available, the opportunity occurred for the direct confirmation of the hypothesis that the metabolism of lead is analogous to that of calcium. Hunter and Aub (1926) kept patients with chronic lead poisoning on a low calcium diet, and then gave them parathormone, with a view to determining the total output of calcium and of lead. For, under these circumstances, any large and prolonged rise in the blood calcium and in the calcium excretion would occur at the expense of the skeleton, and it was of interest to discover whether or not the lead deposits would be mobilized with the calcium.

Parathormone definitely increased the excretion of lead when first given. The amounts excreted were far greater than those obtained when potassium iodide, ammonium chloride, or phosphoric acid were given. When parathormone was given a second time, little or no increase in lead excretion was observed, though the extract was known to be potent because it produced its characteristic effects on calcium metabolism. Evidently parathormone rapidly and effectively mobilizes from the bones a certain amount of stored lead which is readily available. The remaining lead is mobilized much more slowly in the normal routine of metabolism. In six patients studied, the rapid mobilization and elimination of large amounts of lead produced no ill-effect. However, the procedures employed were very drastic, and, used without due care, might produce the acute toxic episodes of plumbism. The action of parathormone in lead poisoning confirms the theory that there is a striking parallelism between the storage and excretion of calcium and of lead.

Storage of other elements in bone. There is a tendency for the selective localization in bone not only of lead, but also apparently of arsenic (Brouardel, 1896), mercury (Kobert, 1906), lithium (Stoeltzner, 1908), strontium (Desgrez and Meunier, 1927), silver (Gettler, 1927), and radium. In 1929 Flinn and Seidlin used parathormone in an attempt to increase the elimination of radium from the bones in factory workers poisoned by radium and mesothorium compounds. Such poisoning is known to occur where girls employed in painting the dials of luminous watches are in the habit of pointing their brushes with their lips. Necrosis of the jaw and aplastic anaemia may result from the poisoning, alpha radiation being enormously destructive of the bones in which it is stored and also of the adjacent haemopoietic marrow.

Use of Calcium Salts in Therapeutics.

A survey of the results of calcium administration in disease at once shows that, as a therapeutic agent, it has proved disappointing. The constant supply of calcium in the food and the large available store in the bones make it unlikely that the regulating mechanism ever lacks calcium for distribution throughout the body. It is when the function of some part of this mechanism breaks down that the tissues suffer from calcium deficiency. It therefore follows that the use of cod-liver oil, ultra-violet light, irradiated ergosterol, parathyroid or thyroid extract is often of greater value than the direct administration of calcium salts.

Need for a diet adequate in calcium. The use of well-balanced diets is not a necessary counterpart of an advanced civilization. Thus it has been calculated that the diet of the Finns contains between 2 and 6 grm. CaO daily (Tigerstedt, 1910), whereas the equivalent figure for the average diet in the U.S.A. is only 0·45 grm. Sherman (1920) regards this figure with some alarm, since he considers that 1 grm. a day is really required. He urges the use of 'calcium carbonate or phosphate habitually added to human food by mixing

it with table salt . . . or a more liberal use of milk, which is an important source of proteins of high nutritive efficiency and of the fat soluble vitamin as well'.

If, then, a diet containing little calcium is to be regarded as a potential source of harm, how much more harmful must be the food consumed over large areas of China and India. There the diet may be deficient in calcium or phosphorus, may contain an excess of acid-forming over base-forming mineral elements, and, above all, is very likely to be deficient in vitamins or to be consumed by women kept in darkness. A high calcium diet of adequate vitamin content is required by pregnant and lactating women to allow for the drain of calcium into the foetus, and especially through the mother's milk. Owing to the great loss of calcium from the skeleton in exophthalmic goitre, attention should be paid to the mineral content of the diet in this disease.

Tetany. In post-operative tetany success in treatment will vary according to how much parathyroid tissue has been destroyed. Calcium lactate may be employed as a powder, taken fasting in repeated doses up to a total of 10 to 30 grm. daily. These large quantities do not cause abdominal discomfort. Too often a few grains are given, in which case we can hardly expect much effect, since we know that in normal individuals the maximal rise in serum calcium after a dose of 10 grm. is only 14 per cent. (Bauer and Ropes, 1926). More severe cases require parathyroid extract in addition to calcium salts, and even this may be ineffective when extirpation of the glands has been extensive. The onset of laryngeal spasm, bronchial spasm, or convulsions demands intravenous therapy; 20 c.c. of a 5 per cent. solution of calcium chloride may be injected into a vein, and, if given very slowly, no ill-effects are produced. The use of thyroid extract and irradiated ergosterol in post-operative tetany has hardly passed the experimental stage.

Cameron (1924) recommends the intramuscular injection of 1 grain of calcium chloride in infants with laryngismus. In the tetany of rickets or osteomalacia the use of parathyroid extract is contra-indicated excep tin emergency, since the increased serum calcium is brought about by the removal of calcium from the bones, which are already deficient in it. The administration of cod-liver oil or ultra-violet light may be all that is necessary for the proper treatment of the rickets or osteomalacia and for the relief of the tetany.

Lead poisoning. In the prevention of industrial lead poisoning a diet of high calcium content plays its part. In lead works in this country it has for many years been customary to supply the workmen, free of cost, with a glass of milk in the morning. This is empirical treatment of considerable merit, anticipating as it did by many years the discovery that a high calcium intake assists the storage of lead in a harmless form in the bones.

The toxic episodes of lead poisoning—namely, lead colic, lead palsy, and meningo-encephalopathy—may be regarded as urgent indications for calcium therapy. In this country the Home Office Regulations, by control of dusts and fumes, have abolished meningo-encephalopathy, but it would be idle to suppose

that lead colic and lead palsy have disappeared from industry. It is difficult to estimate the death-rate in meningo-encephalopathy; it is probably quite high. Aub (1925) states that of six cases three recovered promptly when given large quantities of milk and calcium lactate, and three died without such treatment. During the development of lead palsy a high calcium diet should be used to favour storage of lead.

After the acute toxic episodes have passed, elimination of lead may be accelerated by the use of a low calcium diet together with ammonium chloride. This is administered cautiously in 1-grm. doses given in a glass of water six or eight times a day. Provided there is no nausea or headache this treatment is continued for two or three weeks, the patient being kept on a diet containing a strict minimum of 100 mg. of calcium a day. Should any toxic episode appear, ammonium chloride must be stopped and a high calcium diet used to favour the storage of lead. It is necessary to emphasize the difference between the use of agents assisting the excretion of lead and those assisting its storage. The acidosis method of lead elimination is so potent that its use during colic or meningo-encephalopathy might prove fatal, from the further mobilization of lead at a time when the reverse procedure is essential in treatment.

Colic. The question of the relief of lead colic by calcium therapy involves more than simply the tendency to favour storage; there is evidently an antispasmodic action on involuntary muscle. The only experimental evidence bearing on this is that of Kennedy (1926) who reported that by increasing the calcium content of the fluid bathing the uterine strip, the result in the uterine muscle was both a loss of tone and of peristalsis. The pain of lead colic is probably due to a contraction of the tonic ring in the intestine with marked peristalsis approaching this. A high calcium diet usually brings relief within forty-eight hours. In severe cases, by the slow intravenous injection of 15 c.c. of a 5 per cent. solution of calcium chloride, it is possible to relieve the pain by the time the injection is over. The patient feels hot and flushed and may vomit. The effect on the pain is very striking and is far superior to that of any other means of therapy. Should it be necessary, the injection may be repeated in two hours.

By the same method Aub has brought about prompt relief from renal colic and gall-stone colic. Theoretically the relief of spasm should help in the passage of the stone, but this remains to be seen. An additional advantage of this method is that a differential diagnosis between the pain of renal colic and appendicitis can be made, the former being relieved promptly, the latter persisting.

Acute necroses of the liver. The accidental discovery by Minot and Cutler (1928) that a low calcium diet rendered dogs more susceptible to carbon tetrachloride poisoning led them to investigate extensively the chemistry of the blood in acute necroses of the liver.

Carbon tetrachloride causes a severe intoxication in dogs on a meat diet, while the addition of calcium salts to such a diet produces a high degree of

tolerance to the drug. The symptoms of poisoning are gastro-intestinal irritation and hyperexcitability, followed by depression. There is a retention of guanidine in the blood and a hypoglycaemia. The relief and protection given by calcium seem to depend upon its antagonistic effect to the retained guanidine. When calcium is administered to poisoned animals the nervous symptoms are relieved and the blood-sugar is restored to normal. However, if the blood-sugar is raised by the administration of glucose, the hyperexcitability persists until calcium is given in addition. Similar results were obtained in a study of chloroform poisoning in dogs.

The investigation was then carried to liver disease in the human subject, and more especially to eclampsia. Some cases showed hypoglycaemia and guanidine retention, and, where this was the case, prompt symptomatic relief followed the intravenous injection of 10 c.c. of a 10 per cent. solution of calcium gluconate. For example, in a woman with eclampsia who was semi-conscious and blind, within fifteen minutes of the injection the vision was much improved, within forty minutes the sight was restored, and the blood-sugar raised towards normal. Though the number of cases studied was small it is clear that such a highly protective action of calcium salts against liver poisons is worthy of further investigation.

Oedema and inflammatory exudates. French workers, notably Blum (1922), have pointed out the diuretic action of calcium chloride in oedema. This is not a specific effect of calcium ; it apparently results from a change in the balance of ions in the body fluids. Blum maintains that by increasing the calcium ions the sodium ions are decreased, and, since the retention of fluids is closely associated with the retention of sodium, the oedema is decreased. Fraser (1927) offers an alternative explanation. He points out that since ammonium chloride acts in a similar manner it is probably the acid properties of these salts which are responsible for their diuretic action, though the calcium may have an effect in the same direction by its antagonistic action to sodium. Blum has extended his observations to inflammatory exudates and has reported beneficial effects in pleural and peritoneal effusions and in conjunctivitis.

Erythema pernio, asthma, and chronic ulceration. The use of calcium salts has long been advocated in erythema pernio, and the apparent success of this treatment has led to its trial in allied conditions such as acro-asphyxia and erythema induratum. In none of these conditions are there any grounds for concluding that calcium therapy might be efficacious. In all of them the serum calcium is normal, and clinical benefit does not follow the administration of calcium alone or combined with parathyroid tablets. In erythema pernio sudden and extreme variation in severity is a clinical characteristic of the condition, and is responsible for the reputation gained by calcium as a curative agent, for in those somewhat rare examples which are persistent calcium therapy proves a failure.

Urticaria is another condition in which calcium administration has been widely practised. Wright (1896) was the first to advocate its use on the

grounds that in sufferers the coagulation time of the blood is diminished, and that possibly urticaria is due to a diminution of the serum calcium. Briggs (1923), Greenbaum (1927), and others have shown that the serum calcium is normal in cases of urticaria. White (1914) reported twenty-three cases treated with calcium lactate: only half of them showed satisfactory improvement. In 1928 Burgess showed that when dermographism is the predominant feature the case responds rapidly to calcium salts; when dermographism is not marked treatment with calcium salts produces no striking benefit. It may, therefore, be accepted that calcium is not of general value in urticaria, but cases do occur in which it is exceedingly useful. Nevertheless calcium salts, as usually given, do not increase the coagulability of the blood, and defective coagulation has no immediate relation to the occurrence of the wheals. Calcium has also been employed in a number of conditions allied to urticaria. It has been recommended for hay fever (Chiari and Januschke, 1910) and the coryza of iodism (Emmerlich and Loew, 1915). Calcium therapy in asthma was first recommended by Kayser (1914) and since then many enthusiastic reports as to its value in this condition have appeared. Most of these observations have been made without controls, and, without exception, they fail to carry conviction.

Ten years ago, the treatment of chronic ulceration with calcium and dried parathyroid extracts achieved considerable prominence, particularly for varicose ulceration. Grove and Vines (1921), claimed that what they called the 'ionic' calcium of the serum, as estimated by the method of Vines, was lowered in such conditions, and returned to normal when calcium salts were given by the mouth or as intramuscular injections, along with dried parathyroid extracts. There have been many criticisms of this work. No proof was forthcoming that the so-called fall in blood calcium had any causal relation to the ulceration. The method of Vines for estimating 'ionic' calcium was a biological one, so that it is impossible to compare the results with those obtained by chemical methods. Moreover, the clinical optimism aroused has not been justified by ultimate results. Luff (1928) in a collective investigation showed that calcium and parathyroid administration has no beneficial effects. Out of 235 varicose ulcerations in which such treatment was given only 94, or 40 per cent., healed; out of 857 in which this treatment was not given, 562, or 65 per cent., healed. In both groups of patients suitable local treatment was given.

Milk fever of cows. The essential clinical feature of 'parturient paralysis' or 'milk fever' of the cow is tetany. It may be confined to the hind limbs or it may be generalized. It is followed by deep coma and often by death. The cause of the condition is uncertain, but acute hypocalcaemia, probably from the calcium drain by lactation, is the determining cause of the symptoms (Little and Wright, 1925; Dryerre and Greig, 1928). In its treatment inflation of the mammary gland has been practised for many years. It is now known that mammary inflation produces a rapid and regular rise in the blood calcium, and that this rise is concurrent with, and bears a direct relation to, the disappearance

of the symptoms of the disease. Intravenous and subcutaneous injections of calcium gluconate have been used successfully in treatment (Greig, 1930). It has been shown in the sheep that 'lambing sickness' or 'ewe distemper' is identical in its essential pathology with 'milk fever' in the cow (Greig, 1929).

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STUDIES ON ACHLORHYDRIA AND ANAEMIA[1]

By DANIEL T. DAVIES
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With Plate 22

THE relationship of achlorhydria to anaemia has become more apparent within recent years, and many important observations have been made on this interesting connexion. While the exact proof of cause and effect is as yet unsolved, there can be no doubt that both primary anaemia and secondary anaemia are known to be accompanied by an achlorhydria: but while achlorhydria is an almost invariable finding in the primary or Addisonian type, it is only present in a certain proportion of cases of secondary anaemia. The first observation to be made on the gastric secretion in pernicious anaemia appears to have been made as long ago as 1850 (1) and with this early work the name of Fenwick (2) is closely connected. But it is only within comparatively recent times that the presence of achlorhydria has been noted in secondary anaemia, and among the earliest investigations conducted in this direction were those of Faber (3) and his school.

That the achlorhydria, or rather that the gastric lesion indicated by the achlorhydria, found in primary anaemia is the underlying cause for the development of the malady is now gaining acceptance, and among the reasons for this view may be mentioned—the finding of achlorhydria years before the presence of anaemia, the constancy of the achlorhydria even after the restoration to complete health by means of liver administration, and lastly the important observations of Castle (4). Indeed the view of Fenwick that the achlorhydria is only an index of the gastric atrophy, and the anaemia the sequel of such atrophy, has been confirmed by these most recent observations.

Support to this hypothesis of pernicious anaemia being the result of a gastric defect has been found in an anaemia of pernicious type with carcinoma of the stomach, and in some cases of gastrectomy (5 and 6), and in the still rarer finding of subacute combined degeneration of the cord in cancer with achlorhydria (7). But whilst there is evidence that the abnormal gastric condition is the precursory factor in the development of Addisonian anaemia, the association between achlorhydria and secondary anaemia, or rather the nature of this relationship, is by no means so clear. Some authors have attributed the achlorhydria to the anaemia and cite the achlorhydria that follows haematemesis

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in cases of gastric ulcer, or the achlorhydria that follows advanced anaemia due to bleeding piles, as examples of achlorhydria secondary to the anaemia and a direct result of the anaemia. That such an explanation is not true is shown by the frequent finding of achlorhydria with marked secondary anaemia in cases in which there has been no loss of blood; and sufficient work has appeared within recent years to show that anaemia occurs with greater incidence in a group presenting achlorhydria than in others with a normal gastric secretion (8). Why some individuals with achlorhydria show no departure from the normal blood picture, and why some show a secondary and others a primary anaemia are questions to which no definite answer is as yet forthcoming.

Studies on the gastric secretion have been mostly confined to the presence or absence of free acid, and as the usual method, although standardized and highly serviceable, means the introduction of a diluent in the form of gruel, changes in the gastric secretion have been to a certain extent masked. It was thought that if closer study was made on the undiluted gastric secretion that some differences might possibly be found to account for the types of anaemia. With this end in view a number of patients with achlorhydria were investigated by means of histamine. The gastric secretion was correlated with the clinical state and the blood picture, and this paper deals with these observations. Here achlorhydria is taken to mean absence of free HCl throughout the period of an ordinary fractional gastric analysis. It is to be remembered that this is only a relative term, for it is well known that a patient showing this state of achlorhydria may still secrete free HCl following the subcutaneous injection of histamine while another (such as a case of pernicious anaemia) may be quite unable to secrete acid after the strongest stimulation. The term is therefore, although convenient in its comprehensiveness, of little value in itself, for it includes both temporary and permanent states and fails to offer any distinction between these forms. The term achylia is used in this paper only when it has been proved that the gastric secretion contains no ferments as well as no acid secretion.

The gastric juice was examined in the fasting state and after the subcutaneous injection of histamine. The dose of histamine given varied between 0·3 and 0·5 mg., and the juice was aspirated at ten and twenty minutes following the injection. With care in the introduction of the tube, and seeing that it was not of such length as to coil in the pyloric antrum, the juice was seldom bile stained. It was found, however, that if the patient was materially disturbed and much nausea induced by swallowing, the tube bile was far more frequently obtained. Those few cases that showed bile in their resting juice were discarded. In addition to noting the acidity the ferment content was also estimated, and the latter observation was done on the lines of Fuld's edestin method. The figures given for the acid are in terms of N/10 NaOH—and those of pepsin as the dilution of gastric juice necessary to digest 1 c.c. of 0·1 per cent. solution of edestin in N/30 HCl. The pH of the gastric juice was

obtained by colorimetric methods. In the three samples of gastric juice in addition to noting the pH, the HCl and ferment content, note was also made of the appearance of the juice whether clear or cloudy, of the mucus content whether excessive, normal or diminished, and of the presence or absence of a whitish deposit on standing.

According to this plan of study the following table gives the details obtained of the resting juice, and the samples withdrawn at ten or twenty minutes intervals after the subcutaneous injection of histamine in a *normal* person.

	Resting Juice.	Histamine.	10 minutes.	20 minutes.
Volume	28 c.c.	0·5 mg.	38 c.c.	48 c.c.
Appearance	clear		clear	clear
Mucus	nil		nil	nil
Deposit	nil		nil	nil
pH	−3		−3	−3
HCl	22		46	63
Pepsin	286		512	600

All the patients chosen for the investigation were known to have achlorhydria—some exhibiting a primary anaemia, others a secondary anaemia, and others showed no apparent departure from normal.

Forty-five individuals were examined:

Group A.	Pernicious anaemia . . .	15
Group B.	No definite clinical entity . .	5
Group C.	Secondary anaemia . . .	15
Group D.	Achlorhydria but no anaemia .	10
		45

Group A. *Pernicious Anaemia.*

As already noted, Fenwick appears to be one of the first clinicians to draw attention to the advanced atrophic condition of the gastric mucous membrane in this disease, but it is doubtful whether the distinction between the achylia resulting from such a lesion and achlorhydria has been sufficiently realized. Some writers have used the terms as synonymous, and especially is this true of Continental observers. The difference between the two terms should be appreciated—for achlorhydria means absence of demonstrable HCl during the ordinary fractional analysis, while the term achylia should be reserved for that state in which there is an absence of ferments as well as acid. As the estimation of the gastric ferment—pepsin—is a comparatively long process, this may account for the relative scarcity of observations on pathological states as compared with the HCl determinations in these conditions.

The respective details of the fifteen cases are given in Table I.

They were all undoubted cases of pernicious anaemia—three were examined while very anaemic (Cases 13, 14, and 15)—one was a very early case (Case 10),

TABLE I

Group A. Primary Anaemia

Case No.	Age.	Sex.	General State.	Gastric Analysis. Resting Juice.						Gastric Analysis. 10 minutes after Histamine.						Gastric Analysis. 20 minutes after Histamine.						Remarks.
				Vol.	Mucus.	Deposit.	pH.	HCl.	Pepsin.	Vol.	Mucus.	Deposit.	pH.	HCl.	Pepsin.	Vol.	Mucus.	Deposit.	pH.	HCl.	Pepsin.	
				c.c.						c.c.						c.c.						
1	38	M	Good. No anaemia	35	nil	+++	8	0	0	18	nil	+++	8	0	0	6	nil	+++	8	0	0	Liver 3 years
2	48	F	Good. No anaemia	30	nil	+++	8	0	0	16	nil	+++	8	0	0	7	nil	+++	8	0	0	Liver 2 years
3	39	M	Good. No anaemia	15	nil	+++	8	0	0	15	nil	+++	8	0	0	7	nil	+++	8	0	0	Liver 3 years
4	49	M	Good. No anaemia	15	nil	+++	8	0	0	12	nil	+++	8	0	0	15	nil	+++	8	0	0	Liver 9 months
5	86	F	Good. No anaemia	20	nil	+++	8	0	0	12	nil	+++	8	0	0	10	nil	+++	8	0	0	Liver 9 months
6	57	M	Good. No anaemia	45	nil	+++	8	0	0	16	nil	+++	8	0	0	5	nil	+++	8	0	0	Liver 3 years
7	59	M	Good. No anaemia	12	nil	+++	8	0	0	5	nil	+++	8	0	0	4	nil	+++	8	0	0	Liver 1 year
8	44	M	Good. No anaemia	40	nil	+++	8	0	8	18	nil	+++	8	0	4	10	nil	+++	8	0	8	Liver 3 years
9	57	M	Good. No anaemia	27	+++	+	8	0	48	7	+++	nil	8	0	180	8	+++	nil	8	0	120	Liver 2 years
10	44	F	'Glossitis'. Reds 3·2. Hb. 80 %	17	nil	+++	8	0	4	15	nil	+++	8	0	8	8	nil	+++	8	0	16	Sore tongue 6 months
11	49	M	Good. No anaemia	40	nil	+++	8	0	0	15	nil	+++	8	0	0	8	nil	+++	8	0	0	Liver 3 years
12	49	F	Neural symptoms. No anaemia	20	nil	+++	8	0	4	12	nil	++	8	0	8	10	nil	+	8	0	32	Liver off and on 3 years
13	40	M	Anaemia + Reds 1·2. Hb. 28 %	25	nil	+++	8	0	0	12	nil	++	8	0	0	10	nil	+++	8	0	0	Fresh relapse
14	56	F	Anaemia + Reds 1·3. Hb. 36 %	10	nil	+++	8	0	0	8	nil	+++	8	0	0	8	nil	+++	8	0	0	Fresh relapse
15	47	M	Anaemia + Reds 1·14. Hb. 35 %	15	nil	+++	8	0	0	12	nil	+++	8	0	0	8	nil	+++	8	0	0	Fresh relapse

one who had not taken liver consistently showed a progressive neural lesion (Case 12), and the remainder were cases which had shown a good return to health with liver therapy—some having been well for the previous 2–3 years.

When the various analyses are examined it is seen that in the majority—in eleven of the cases—the findings are identical, and that in the remaining four (Cases 8, 9, 10, and 12) certain differences are obtained. It may be well to dwell on the findings common to all:

Volume. While the volume of the resting juice varied between 10 and 40 c.c. it was observed that no appreciable increase in the secretion occurred after the injection of histamine. This was noted in all of the cases of this group.

Appearance. As the gastric secretion in this investigation was studied without the introduction of any diluent into the stomach it was possible to make observations on the appearance of the juice—and it was found that in all a cloudiness was observed—which contrasted with a similar specimen obtained from a healthy stomach. This cloudiness was also present in the juice aspirated after histamine injection and could not be completely dispelled either by standing or centrifuging a sample.

Mucus. In only one of the cases (Case 9) was mucus found to be present, in all the other cases its absence was noteworthy. Consequently the samples could be aspirated and pippeted with ease in marked contrast to those cases of achlorhydria with secondary anaemia.

Deposit. When the juices were allowed to stand in test-tubes for an hour or so a whitish deposit formed at the bottom—of about one inch depth from a 20 c.c. volume of juice. This occurred with constancy in all of the cases with exception of Case 9. Microscopical examination of this deposit disclosed masses of epithelial cells of one type—flattened, and having the appearance of squamous cells: in one case the polymorphonuclear white cell was also present in large numbers. The significance of this deposit and the exact structure of these cells will be discussed later. This deposit was found in fourteen of the cases, and in no case as yet examined has such a massive deposit been found, except with absence or great diminution of pepsin secretion.

The reaction of the gastric juice. In none of the cases examined was the pH of the gastric secretion changed by histamine injection; as ten of the cases had returned to normal health with liver, it indicates the permanence of the gastric lesion. The pH was always found to be in the region of 7–8, and free HCl to be absent.

Pepsin estimation. Eleven out of the fifteen cases showed juices possessing no proteolytic power after histamine; this occurred both in those patients who had returned to health and those who were at present anaemic.

It is seen from Table I, that Case 8, a male, aged 44, showed small amounts of pepsin in the three samples of juice—i.e. 0·25 c.c. digested 2 c.c. of 0·1 per cent. edestin solution. The other interesting fact is found in the history he gave—that he had remained quite well for the *past three years with a single*

dose of liver per week. Whether the presence of pepsin indicates a lesser degree of gastric failure, and whether this is responsible for the apparent adequacy of the liver dosage, remains at present only a possibility. Case 9, is still more unusual, for the gastric analysis (Table I) shows an abundance of mucus secretion in addition to a good pepsin content, especially after histamine. With this is found an absence of deposit in the second and third samples, and just a slight amount in the resting juice after centralization. Up to the time of analysis the patient had taken liver four times a week. He was told to cease taking it, and since that date he has remained continuously under observation. Eight months have now elapsed and so far no untoward symptoms have appeared. The blood has also kept within normal limits, the Hb 95 per cent. and the red cells over 5 million. Whatever be the cause of pernicious anaemia it appears that, if the gastric secretion plays any part in its development, this patient does not show at present such an advanced state of atrophic function as the other cases; and if he is able to keep a normal blood picture without further liver therapy it will be an interesting though indirect confirmation of the intimate relationship of Addisonian anaemia to gastric achlyia. Case 10 also showed a small amount of pepsin in the resting juice and increased amounts in the other samples. This patient, a woman, sought relief for a 'sore tongue' and it was only by routine examination that the underlying condition was discovered. The symptoms had only been present for six months and the blood did not show a marked anaemia.

Red cells	3·25 million
Hb. per cent.	80
Average diameter	7·48 μ

The blood slide, however, showed macrocytes.

In addition to the glazed and fissured tongue the tendon reflexes were much exaggerated, and there was loss of vibration sense in the right lower limb. Although the blood picture is not diagnostic the gastric secretion was strongly suggestive in its appearance—the presence of deposit, absence of mucus and uniform pH—to the cases of established pernicious anaemia. A finding peculiar to this case was the large number of polymorph white cells found in the deposit. Polymorphs also were found among the epithelial cells which were of the same nature as those in the other cases. As it was thought that this case was probably a very early one and the presence of white cells indicated some active gastric infection (the mouth was quite clean and the patient edentulous) gastric lavage was performed for a period of three months, and, although no material benefit could be noted, the blood count remained more or less the same:

Red cells	3·7 million.
Hb.	85 per cent.

The patient is now taking liver and her progress will be interesting.

Case 12 is also deserving of attention, for in spite of infrequent liver therapy she shows no progression in her anaemia, although the neural lesion

has progressed steadily during the past three years. In this patient proteolytic ferment is demonstrable in small amounts in the gastric secretion, showing a less advanced degree of disordered function. Whether this accounts for her freedom from a relapse or not is again uncertain.

Group B. *Intermediate Group.*

The five cases possessed to some degree symptoms and signs suggestive of primary anaemia, and others suggestive of a secondary anaemia. As they could not be properly placed in either Group A or C, they are isolated into a separate group for the purpose of description only. (See Table 2).

Case 1, complained of pins and needles in the hands and feet—for which she sought advice. The smooth mucosa of the tongue and the achlorhydria suggested subacute combined degeneration of the cord. But the blood-count showed a well marked secondary anaemia. The average diameter of the red cells was 7·4 μ, although macrocytes were observed in the blood-film. From the table it is seen that the gastric secretion failed to change its reaction and that the pepsin secretion was poor. In addition the mucus secretion was excessive and no deposit was found.

Case 2, was a man known to have achlorhydria with excessive mucus secretion for at least three years, but two years ago he exhibited no anaemia. He showed a mild degree of anaemia with an average diameter of 7·8 μ and macrocytosis. The mucosa of the tongue was normal. The gastric secretion in this individual is poor and closely resembles that seen in pernicious anaemia, except that some pepsin is still being secreted.

Case 3, displayed symptoms indicative of a subacute combined degeneration of the cord, but showed no anaemia. Marked changes were present in the mucosa of the tongue but no other organic signs were obtained. With this indefinite picture a poor gastric secretion was found—the pH being constant, a deposit in the juice and a greatly diminished secretion of pepsin.

Case 4, although incomplete, is of interest in that he possessed a *normal* gastric secretion three years previously. This was investigated on account of haematemesis which occurred some time before. A crater was also demonstrated radiographically. Although the tongue showed no change achlorhydria was found with early blood changes. There was complete absence of mucus and a deposit on standing.

Case 5. The last case of the group, was examined on two occasions. The first time following his appearance on account of flatulence and discomfort after food, and the second, six months later, when he was comparatively well. Twelve months before he had been ill with a fever of unknown origin; the gastric symptoms had began from this date. In addition to an achlorhydria he showed some degree of anaemia.

Reds	3·2 million.
Hb.	64 per cent.
Whites	2,800.

At this time, although showing a secretion of HCl twenty minutes after histamine, the pepsin secretion was absent in the first and second specimens. During the following six months the abdominal symptoms disappeared and the blood-picture became normal, and this occurred without any treatment.

TABLE II

Group B

Case No.	Age.	Sex.	General State.	Tongue Mucosa.	Gastric Analysis. Resting Juice.						Gastric Analysis. 10 minutes after Histamine.						Gastric Analysis. 20 minutes after Histamine.						Remarks.
					Vol.	Mucus.	Deposit.	pH.	HCl.	Pepsin.	Vol.	Mucus.	Deposit.	pH.	HCl.	Pepsin.	Vol.	Mucus.	Deposit.	pH.	HCl.	Pepsin.	
					c.c.						c.c.						c.c.						
1	44	F	Sec. anaemia. Red cells 3·8. Hb. 48 %	Smooth	24	++++	nil	8	0	0	15	+++	nil	8	0	8	10	+++	nil	8	0	16	
2	57	M	Good. Red cells 4·1. Hb. 68 %	Normal	60	nil	+	8	0	0	20	nil	nil	8	0	6	25	nil	nil	8	0	16	
3	61	F	Neural symptoms. Red cells 4·7. Hb. 70 %	Smooth	14	nil	++	8	0	2	7	nil	nil	8	0	12	10	nil	nil	8	0	6	
4	54	M	Good. Red cells 3·9. Hb. 80 %	Normal	15	nil	++	8	0	4													
5	49	M	(*a*) Red cells 3·2. Hb. 64 %	Normal	20	+++	nil	8	0	0	15	nil	nil	8	0	0	12	+++	nil	3	8	120	6 months interval
			(*b*) Red cells 5·8. Hb. 90 %		48	++	nil	8	0	250	30	nil	nil	3	0	250	30	nil	nil	−3	9	250	

The blood figures at this time were:

Reds	5·8 millon.
Hb.	90 per cent.
Whites	7,000.

When the gastric analysis was repeated it was seen (Table II, Case *a* and *b*) that the pepsin secretion had improved. Whether this accounts for the improvement in the state of the blood, or whether these facts are quite unrelated is beyond proof. Histamine demonstrated in the first analysis that the stomach was capable of responding and that the damage was not of such a degree as is found in pernicious anaemia. It is conceivable that the infection the patient suffered twelve months previously played a part in damaging the secreting mechanism of the stomach and that its recuperation is associated with a better blood condition.

Group C. *Achlorhydria with Secondary Anaemia.*

The fifteen cases showed achlorhydria. The respective details are given in two tables.

A study of these cases shows certain common features—some of which are also found in primary anaemia, but there are other features in the gastric secretion as well as in the blood which clearly distinguish the majority from those of Group A. Twelve of the fifteen were women between the ages of 30 and 60. Six of these patients gave histories of excessive bleeding from one source or another—three of them being women who had suffered from periodic menorrhagia, while two other females gave histories of haematemesis, twenty and three years previously. The remaining patient, a male, had a haematemesis three years previously. The three females who had had excessive menstrual loss had no organic uterine lesion. One female had had amenorrhoea for eight years. Nine of the patients gave no symptoms of bleeding in the past or present history. Nine showed definite atrophic changes in the mucous membrane of the tongue and four showed fissures at the angles at the mouth, and almost all the patients complained of frequent 'cracking' of the lip edges. Eight of the cases had an enlarged spleen—to a degree such as is found in pernicious anaemia. With treatment the spleen decreased in size and ultimately receded behind the costal margin. In only one of the fifteen cases were the 'spoon-shaped' nails observed—but all the patients on questioning complained of excessive brittleness of the nails, and some showed a flattening of the nail. A feature of these nails is that they readily split longitudinally and a ridge forms at this point. The one patient (Case 12) showing the spoon-shaped nails voluntarily remarked on the less painful character of her nails following iron administration. Five only complained of neural symptoms suggestive of sub-acute combined degeneration of the cord, but no confirmatory signs were elicited.

Regarding the blood-counts in the group, it is interesting to note that in none was there a leucocytosis. Only two cases showed any appreciable degree of macrocytosis in the blood-films, and of these, one showed a definite improvement with liver therapy (Case 3). The other cases showed the usual secondary anaemia characteristics of a normal or average low diameter.

TABLE III

Group C

Case No.	Age.	Sex.	Gastric Analysis. Resting Juice.						Gastric Analysis. 10 minutes after Histamine.						Gastric Analysis. 20 minutes after Histamine.						Remarks.
			Vol.	Mucus.	Deposit.	pH.	HCl.	Pepsin.	Vol.	Mucus.	Deposit.	pH.	HCl.	Pepsin.	Vol.	Mucus.	Deposit.	pH.	HCl.	Pepsin.	
			c.c.						c.c.						c.c.						
1	36	F	10	+++	nil	8	0	0	—	—	—	—	—	—	—	—	—	—	—	—	
2	30	F	15	+++	nil	8	0	10	12	+++	nil	8	0	4	10	+++	nil	8	0	6	
3	47	F	35	+++	nil	8	0	16	16	+++	nil	6	0	6	20	+++	nil	−3	40	186	
4	46	M	(*a*) 24	nil	++	8	0	0	15	nil	nil	8	0	4	25	nil	nil	8	0	0	Anaemia present
			(*b*) 15	nil	+	8	0	0	22	nil	+	8	0	0	18	nil	nil	8	0	0	No anaemia } 3 months
5	50	F	25	+	+	8	0	0	15	nil	nil	8	0	0	9	nil	nil	8	0	0	
6	65	M	8	+++	nil	8	0	32	10	++	nil	8	0	64	10	+++	nil	8	0	60	
7	34	F	7	+++	nil	8	0	32	6	++	nil	8	0	64	15	nil	nil	6	0	32	
8	34	F	20	+++	nil	8	0	32	18	+++	nil	6	0	80	25	nil	nil	−3	14	128	
9	48	F	15	+++	nil	8	0	0	34	+++	nil	6	0	40	20	+++	nil	5	0	16	
10	67	F	10	+++	nil	8	0	32	12	+++	nil	5	0	350	5	nil	nil	−3	10	256	
11	58	M	10	nil	+++	8	0	0	8	nil	++	8	0	0	5	nil	++	8	0	0	
12	37	F	12	+++	nil	8	0	64	—	—	—	—	—	—	—	—	—	—	—	—	
13	54	F	20	+++	nil	8	0	120	25	++	nil	8	0	60	35	+++	nil	8	0	128	
14	48	F	20	nil	++	8	0	0	18	nil	++	8	0	0	20	nil	++	8	0	0	
15	44	F	15	+++	nil	8	0	0	12	+++	nil	−3	10	64	8	+++	nil	−3	12	90	

TABLE IV

Group C

Case No.	Appearance of Tongue Mucosa.	Spleen.	Red Cells in Millions.	Haemoglobin %.	White Cells.	Character of Blood Film.	Average Diameter of Red Cells.	History of Haemorrhage.	Nervous System Symptoms.
1	Normal	Not palpable	4·8	48	5,800	Sec. anaemia	—	Menorrhagia	nil
2	Glazed	Palpable	3·7	48	4,200	Sec. anaemia	—	nil	nil
3	Glazed	Palpable	2·6	45	4,600	Macrocytes +	7·8 μ	nil	nil
4	Glazed	Palpable	5·42	60	6,000	Sec. anaemia	—	nil	nil
5	Glazed	Palpable	4·3	66	7,200	Sec. anaemia	7·1 μ	nil	++
6	Normal	Not palpable	3·7	40	7,400	Sec. anaemia	7·1 μ	Haematemesis 3 years previously	nil
7	Normal	Not palpable	3·7	47	6,000	Sec. anaemia	7·1 μ	nil	nil
8	Normal	Not palpable	4·5	65	—	Sec. anaemia	7·5 μ	Menorrhagia	nil
9	Glazed	Palpable	4·2	58	6,500	Macrocytes +	7·8 μ	Haematemesis 24 years previously	++
10	Normal	Not palpable	3·4	37	—	Sec. anaemia	7·1 μ	Haematemesis 3½ years previously	nil
11	Normal	Not palpable	3·26	38	6,200	Sec. anaemia	—	nil	++
12	Glazed	Palpable	3·3	30	5,300	Sec. anaemia	7·3 μ	Menorrhagia	++
13	Glazed	Palpable	3·35	60	6,500	Sec. anaemia	7·1 μ	nil	++
14	Glazed	Not palpable	3·9	44	4,600	Sec. anaemia	7·02 μ	nil	nil
15	Glazed	Palpable	3·5	36	4,300	Sec. anaemia	7·1 μ	nil	nil

Turning to the gastric secretion it is seen that there was an excessive secretion of mucus in all but four, the exceptions being Cases 4, 5, 11, and 14. In these four cases there was a bigger departure from normal in that the pH was constant, the secretion contained *no* pepsin (Case 4 showed 4 units on first examination) and in two a deposit was obtained. Six of the cases showed a fall in pH after histamine. In four of the six cases free HCl was demonstrable—in the others, nine in number, no free HCl was demonstrable. In only four of the cases was the pepsin found in concentration above 100 units. In three it was absent throughout, while in the other cases, eight in number, it varied between 0 and 100 units. A fall in pH occurred in two cases without a simultaneous appearance of free acid. It is seen that those patients who showed a fall in pH and also free HCl showed a better secretion of pepsin than those with a uniform pH (Contrast Cases 10 and 13).

The findings in cases 4 and 11 are worthy of special emphasis. The former shows that it is possible to meet a secondary anaemia accompanied by a gastric secretion identical with that obtained in pernicious anaemia, and that it is a permanent one—present when the patient has returned to normal health—again akin to the gastric achylia of pernicious anaemia. The change that has occurred in the secretion of Case 11 is interesting in view of the fact that he now has complete achylia and absence of mucus, although three years previously his gastric secretion contained an abundant excess of mucus, and in addition he is now forced to take liver to remain well.

It is of some interest to compare the improvement in the blood-picture with the gastric secretion of some of those patients who have been observed for a sufficient length of time, and especially to note the action of liver or iron.

Case 2, of the group has been under occasional observation for a period of two years, but owing to some peculiar trait attends only when dyspnoeic because of her anaemia. She is given iron each time, but the blood-count at the end shows no improvement on the initial level, proving that continued dosage is necessary for a prolonged period.

Reds	4·8 million.		Reds	3·75
Hb.	40 per cent.	Twelve months.	Hb.	48 per cent.
Whites	5,200	Irregular iron therapy.	Whites	4,500
Av. diam.	6·9			

Case 3, showed a good response with liver extract, although the initial blood-count did not possess characteristics of a primary anaemia.

Reds	2·6		Reds	4·0
Hb.	45 per cent.	Two months.	Hb.	70 per cent.
Whites	4,600	Liver extract.	Whites	5,200

Case 4. The only male of the series who was observed for any length of time showed a quick response to iron administration. With the improvement in the anaemia the spleen became normal in size, although the gastric secretion showed no change.

Reds	5·42		Reds	5·73
Hb.	60 per cent.	Two months.	Hb.	95 per cent.
Whites	6,000	Iron therapy.	Whites	7,200

Case 7, showed an equally good recovery with iron therapy with a corresponding improvement in the symptoms.

Reds	3·7		Reds	4·5
Hb.	47 per cent.	Two months.	Hb.	75 per cent.
Whites	6,000	Iron therapy.	Whites	7,000

Case 10. In spite of being 67, this patient showed similar improvement with iron.

Reds	3·45		Reds	4·5
Hb.	37 per cent.	Two months.	Hb.	75 per cent.
Av. diam.	7·1	Iron therapy.		

Case 11 quickly responded to liver extract, although the anaemia was of the secondary type. When he was first seen his gastric juice was full of mucus—a little over three years previously; now his secretion is identical with that seen in a primary anaemia. After the initial improvement liver therapy was withheld for a period of just less than eight months, and a secondary anaemia of equal severity developed to respond again to liver extract.

Reds	2·6	Three months.	Reds	4·15
Hb.	26 per cent.	Liver extract.	Hb.	80 per cent.

Case 12, showed a quick response to iron—and contrasts with Case 2, both in the persistence of continued iron intake and in the end result.

Reds	3·3		Reds	5·1
Hb.	30 per cent.	Six weeks.	Hb.	80 per cent.
Whites	5,200	Iron therapy.	Whites	8,000
Av. diam.	7·1			

From these few results it is seen that some show a definite and quick improvement after iron administration: these were cases in which the red cells were not greatly reduced. Two of the series showed improvement on liver extract. These two showed a greater fall in red-cell level, and one in addition a gastric achylia.

Group D. *Achlorhydria with no Anaemia.*

Tables V and VI give the respective details of the individual cases.

As in Group C, the ten patients of this group complained of abdominal symptoms of long duration. Investigations were all negative in character, except for the common finding of achlorhydria. Nine were females and one male. None gave a history of bleeding from any mucous membrane. One only showed any change in the mucous membrane of the tongue, and the spleen was not palpable in any. No nail changes were observed. From Table VI it is seen that the lowest red-cell level is 4·3 and the lowest haemoglobin 75 per cent., i.e. anaemia was not found in any of these cases.

The quantities of juice (Table V) are greater than in Groups A or C. Six out of the ten cases (5–10 inclusive) showed good secretion of HCl following histamine injection.

Of the four cases which showed no free HCl. after stimulation it is seen that the pH fell in two. Stating this fact in another manner—eight of the ten

TABLE V. *Group D*

Case No.	Age.	Sex.	Gastric Analysis. Resting Juice.						Gastric Analysis. 10 minutes after Histamine.						Gastric Analysis. 20 minutes after Histamine.					
			Vol.	Mucus.	Deposit.	pH.	HCl.	Pepsin.	Vol.	Mucus.	Deposit.	pH.	HCl.	Pepsin.	Vol.	Mucus.	Deposit.	pH.	HCl.	Pepsin.
			c.c.						c.c.						c.c.					
1	40	F	25	++	nil	6	0	500	15	+	nil	4	0	380	20	+	nil	3	0	500
2	45	F	32	nil	nil	8	0	48	15	nil	nil	6	0	20	9	nil	nil	3	0	350
3	47	F	10	++	nil	8	0	128	15	++	nil	8	0	128	20	+	nil	8	0	128
4	47	F	20	++	nil	8	0	64	25	+	nil	8	0	64	35	+	nil	8	0	128
5	48	F	25	nil	nil	5	0	120	15	nil	nil	−3	30	120	20	nil	nil	−3	42	128
6	38	F	15	+++	nil	4	0	250	20	+	nil	−3	12	500	15	nil	nil	−3	30	512
7	34	F	15	++	nil	8	0	96	20	nil	nil	8	0	250	15	nil	nil	−3	10	380
8	60	F	8	++	nil	4	0	500	10	nil	nil	−3	63	520	15	nil	nil	−3	88	350
9	40	F	15	nil	nil	8	0	16	20	nil	nil	−3	52	256	45	nil	nil	−3	82	256
10	65	M	45	++	nil	8	0	256	40	+	nil	−3	125	250	25	nil	nil	−3	96	250

TABLE VI. *Group D*

Case No.	Appearance of Tongue Mucosa.	Spleen.	Red Cells in Millions.	Haemoglobin %.	White Cells.	Character of Blood Film.	Average Diameter of Red Cells.
1	Normal	Not palpable	5·02	90	—	nil abnormal	—
2	Normal	Not palpable	4·57	90	8,200	nil abnormal	7·48μ
3	Normal	Not palpable	4·7	90	—	—	7·1μ
4	Normal	Not palpable	4·3	75	5,000	nil abnormal	7·1μ
5	Normal	Not palpable	4·3	82	4,800	nil abnormal	7·1μ
6	Normal	Not palpable	4·5	75	7,600	nil abnormal	—
7	Normal	Not palpable	4·7	85	8,200	nil abnormal	—
8	Glazed	Not palpable	4·9	80	5,600	nil abnormal	7·3μ
9	Normal	Not palpable	4·8	92	8,200	nil abnormal	7·1μ
10	Normal	Not palpable	4·6	85	8,400	nil abnormal	7·1μ

cases showed a change in reaction following histamine injection. Again it is seen from the table that the secretion of pepsin is good in all and that the resting juice from all the patients showed some quantity of the ferment.

The Deposit obtained in Achylia.

It was found in all the cases but one of Group A, and in two cases of Group C. It does not seem to occur in any juice in which there is an increased secretion of mucus, and occurs only in those in which there is no HCl and no pepsin. Those cases which showed no HCl and a uniform pH of 7–8, but which secreted demonstrable pepsin contained no appreciable deposit. Its constancy is worthy of note—for if a juice is aspirated and found to be cloudy in appearance, to be free of mucus and to deposit a whitish mass, it can be reasonably predicted that it contains no HCl and no pepsin; in other words, that it is an example of true achylia. A search of the literature shows that attention was drawn to this deposit in 1908 by Bassler (9) who recorded the finding of large epithelial cells in the gastric secretion of two cases of achylia with anaemia. Microscopical examination of this deposit shows it to be composed of masses of large flattened cells which stain readily with either methylene blue or haemotoxylin and eosin. The nucleus is small and circular and the cytoplasm is clear, the whole appearance suggesting a squamous cell. In all of the cases the same cell type was observed.

It appeared at first that these cells must have come from the gastric mucosa, but later the oesophagus and pharynx became the more probable source. In a post-mortem examination of a case of pernicious anaemia it was seen that while the films of the oesophagus were identical with those of the deposit in life—those from the post-mortem stomach were of two kinds, squamous and columnar, but mostly columnar. From these observations it is most probable that these cells are oesophageal in origin. It was also found that if some HCl and pepsin were added to the juice containing the deposit that the *deposit* disappeared or was digested, and also that when the deposit was transferred from its achyliac juice to a normal gastric juice that it again disappeared on incubation.

It appears justifiable therefore to state that in a case of pernicious anaemia (or of achylia) the oesophageal and pharyngeal cells, when they are carried down into the stomach, are not digested as in normal cases and are found in sufficient numbers to form a deposit, and they therefore become of some diagnostic value. Photographs of these cells are seen in Pl. 22, Figs. 1 and 2. Emphasis must be placed on the quantitative nature of the test rather than the qualitative—for if a normal juice is centrifuged one or two flat cells may be seen—but in the juices of the cases of pernicious anaemia they are so abundant that no centrifuging is necessary.

Stages in the Failing Gastric Secretion.

The following table gives the stages in failing secretion:

Normal Juice.
Clear. Mucus slight. No deposit. HCl+. Pepsin+.
After histamine—increase in volume, in HCl, and in pepsin.

1st Stage.
Clear. Mucus++. No deposit. HCl diminished. Pepsin+.
After histamine—increase in volume, in HCl, and in pepsin.

2nd Stage.
Clear. Mucus+++++. No deposit. HCl absent. Pepsin diminished.
After histamine—increase in volume slight, increase in HCl and pepsin.

3rd Stage.
Cloudy. Mucus+. Slight deposit (in resting juice). HCl absent. Pepsin absent.
After histamine—little increase in volume. *No HCl.* Pepsin increased.

4th Stage and final stage. *Gastric Secretion in Pernicious Anaemia.*
Cloudy. Mucus nil. Deposit++++. HCl absent. Pepsin absent.
After histamine—no increase in volume. No HCl. No Pepsin. Constant pH.

The Relationship of the Anaemias to Achlorhydria.

The two types, primary and secondary anaemia will be discussed in relation to their gastric secretion and the clinical features correlated with the changes in secretion.

Secondary anaemia with achlorhydria. Many investigators have drawn attention to the secondary anaemia which occurs in certain cases of achlorhydria. Faber (10) drew attention to the association, and many Continental observers (11) have recorded their studies. An excellent review of the literature and observations on the therapeutic value of iron has recently been published by Witts (12). His studies include an analysis of fifty cases of this syndrome, which he calls simple achlorhydria anaemia.

The condition appears not uncommon, especially in women between the ages of 35 and 50. Any out-patient department seems to contain a number of these cases, though the picture is often ill-defined. The patients seem to have a host of symptoms, and it would not be difficult to make a hasty diagnosis of gastric neurosis in a large proportion of them. Their gastric symptoms have persisted for years—sometimes displaying relief with acids, sometimes with alkalis. Pain is rarely complained of, the chief symptoms being morning nausea, flatulence, and a sense of fullness after food. Their appetite is unstable and easily appeased. An inquiry into their diet shows that they seldom partake of any meat, and they readily confine their diet to milk and carbohydrate food. Although superficially the sallowness of the complexion resembles that seen in pernicious anaemia the symptoms of dyspnoea and palpitations are more obvious and distressing in proportion to the blood condition. The relatively lower haemoglobin content probably accounts for the earlier appearance of these symptoms. The sclerotics are often a bluish tint and this

appearance when combined with the sallowness of the face and loss of elasticity in the flesh make a characteristic clinical picture. The lips are often fissured, and the patients remark how easily the lips crack at the angles of the mouth. Changes in the tongue mucosa are common, and in some appear as advanced as those seen in pernicious anaemia or in that syndrome 'dysphagia with anaemia'. The tongue appears flat, the papillae have atrophied, and when the mucosa has thinned right out the muscle underneath gives a reddened angry appearance to the tongue. With splitting in the mucous membrane localized areas of infection give rise to the sore tongue identical to that in pernicious anaemia. The spleen is often palpable, and this disappears with improvement in the anaemia. No excess of bile pigments appears in the blood serum and urobilin is absent from the urine. While the spoon-shaped nail was only found in one of the cases of this series, flatness of the nail was rather a common finding and the majority of the women of Group C, complained of sore and brittle nails.

Menorrhagia was present in three of the anaemic women, and in one this symptom has certainly improved with improvement in the anaemia. The anaemia is not the direct consequence of loss of blood, for in the majority of the cases here recorded the anaemia existed without any apparent cause, and in one of the patients amenorrhoea had been present for many years. Symptoms suggestive of subacute combined degeneration of the spinal cord are not uncommon, but in none included in this series was there any confirmatory sign of a nerve lesion. Constipation seems to be more common than diarrhoea.

Does the abnormal gastric secretion play any dominant part in the development of this secondary anaemia? It has already been shown that the colour index is below 1 and that the majority of the cases show the classical picture of secondary anaemia with either a normal white cell count or a leucopenia. It was seen that only two patients exhibited macrocytes in their blood-films, and in these the average diameter of the red cells was on the high side of normal, 7·8 μ. The majority, however, showed red cells normal in size or variations towards the small size. The main deficiency seems to be in the haemoglobin content. It is possible that the low haemoglobin content may result from a failure of iron absorption or intake. To support the view of defective iron intake the abnormal diet and the abnormal gastric secretion must be considered. Questioning almost invariably reveals the fact that the diet is very poor in protein and that many of the women of this class have not partaken of any red meat for years. And with this defective intake there is a concomitant excess secretion of mucus from the gastric mucosa. If this catarrhal change in the mucous membrane is present in the intestine defective absorption may be the real cause of this anaemia. It is to be expected that any anaemia showing a marked reduction in the haemoglobin per cent. should improve on iron administration, but the fact that the improvement is only temporary and maintained only with continuous dosage is very suggestive of lack of absorption as being the primary factor. The cases shown in Group C demonstrated

how necessary it is to persevere with iron, and that those patients who discard it after a short course do not recover a good haemoglobin level.

In the one male case (Case 4, C) who showed a rapid response with iron salts the gastric secretion remained stationary and showed no better secretion when the patient was fit and well.

Two of these cases of secondary anaemia showed a definite improvement on liver, and one of them (Case 11, C) now has shown a gastric secretion identical with that seen in pernicious anaemia. In these two cases macrocytosis was a prominent feature of the blood films. Improvement on liver, macrocytosis in the blood films and an achylia make the condition simulate closely the primary type although the Colour Index is never above 1. It appears that when the gastric secretion is greatly impaired these intermediate grades of anaemia are also possible. But it can be stated that the type of secondary anaemia, in which there is no apparent cause, and in which there is an achlorhydria with excess of mucus secretion and diminution of ferment content, appears to respond to iron administration. Those cases in which in addition there is a greater disturbance of gastric secretion, a marked reduction in red cells and macrocytosis in the blood films, may also show improvement with liver administration.

The tongue mucosal changes, and the changes in the nail are features highly suggestive of a widespread nutritional disorder, while the recession of the enlarged spleen suggests that its function in enlargement is corrected with iron.

Primary or pernicious anaemia and achlorhydria. Although much has been written on the achlorhydria that is found in pernicious anaemia it seems that sufficient credit has not been given to some English clinicians, and especially to Samuel Fenwick. In most books on pernicious anaemia only a cursory remark is made on Fenwick's description of the atrophic state of the gastric mucous membrane found in this disease. While it is granted that possibly Handfield Jones (1) was the first to draw attention to this, Fenwick's studies extended over a number of years and culminated in a book which appeared in 1880 (2).

His criteria for the diagnosis were :—(1) A progressive anaemia without any apparent cause. (2) Persistent flatulence and anorexia. (3) Temporary improvement with arsenic. (4) A fatal termination. And through post-mortem investigations he showed :—(1) That there was marked atrophy of the mucous membrane of the stomach. (2) That this mucous membrane was incapable of secreting either acid or pepsin.

Without entering into a discussion as to the cause of the deranged gastric secretion in pernicious anaemia it may be said that it is the most advanced that can be met with, that it is permanent, and that it generally results in a complete absence of pepsin. That it has taken years to develop seems reasonable, but the causes do not appear to be the same as those operating in the development of secondary anaemia with achlorhydria. The gastric

symptoms are less marked and the lesion appears to develop in a more latent fashion. That one can merge into the other is shown by one case (Case 11, C) where the achlorhydria and excess of mucus secretion have now been replaced by a secretion identical with that seen in pernicious anaemia.

Since the observations of Fenwick no further light has been shed on the relationship of achylia to primary anaemia until the appearance of the brilliant researches of Castle and his co-workers of Boston (13). Without entering into detail it seems that the normal gastric mucosa secretes some thermolabile substance capable of acting in a neutral solution on beef muscle in such a way that a remission can be produced in a case of pernicious anaemia through the absorption of the product so formed. Castle has shown that this hypothetical substance is present even in the juice of some patients with achlorhydria (who are not suffering from pernicious anaemia). His experiments seem to show that this substance is not pepsin, but it is suggested by Castle that it may be rennin. The estimation of pepsin in the present series shows that, while it is completely absent in the majority of cases of pernicious anaemia, it is not invariably absent, and that in two cases of secondary anaemia it was as completely absent. That this hypothetical (?) ferment of Castle fails, as when pepsin fails to be secreted, appears to be true in the majority of cases, but if we are to accept Castle's views it appears that in some cases one fails without the other. It seems only a step from Fenwick's work to that of Castle although 70 years intervened—one seems a logical step to the other—Castle establishing the dependance of the bone-marrow on the gastric secretion—a view that had already been suggested and partly supported by the direct observation of Fenwick.

Minot (14) has drawn attention to the varying dosage of liver necessary to keep patients with pernicious anaemia well, some requiring far more than others. In this connexion it is interesting to recall that one of the long-standing cases of Group A kept quite well on one liver sausage per week, and this man was able to secrete some pepsin; while another whose pepsin secretion was good has now remained in excellent health for eight months without liver, while another of the series, a man who first relapsed in 1929 and who shows a complete achylia, immediately experiences a sore tongue if he is unable to ingest liver three times a week.

But for Castle's experiments it would be almost natural to conclude that the proteolytic ferment pepsin is the essential intrinsic factor, but his work demonstrates that it is some other as yet unisolated product of gastric secretion. That it fails with the failure of gastric secretion seems the rule, and it seems a kindness of nature that it is the last or one of the last to fail—for if all the patients who fail to secrete HCl failed also to secrete this substance pernicious anaemia would become a more common disease.

Summary.

A study of the gastric secretion in a number of cases of achlorhydria shows that there are degrees of impairment, the most advanced being that found in primary or pernicious anaemia.

Some patients, although showing achlorhydria on ordinary gastric analysis, show a good proteolytic secretion following stimulation with histamine. These patients as a rule do not show any constitutional effects as the result of their minor gastric impairment.

A further stage is found in those patients who show a secondary anaemia. In these there is an excessive mucus output, a diminished pepsin content, and in some cases a fixture of the pH.

The syndrome of achlorhydria with secondary anaemia is a distinct clinical entity. With the enlargement of the spleen the atrophic changes in the mucosa of the tongue and the symptoms of anorexia and flatulence the clinical picture is analogous to pernicious anaemia. In the majority of the cases the examination of the blood readily establishes the diagnosis.

The response of these cases to iron and the necessity for continued dosage with it are suggestive of delayed and defective alimentary absorption. The disease appears to be more common than the primary anaemia.

Intermediary grades are found, and in these the anaemia may possess both primary and secondary characters, both in diagnostic and therapeutic features.

In primary anaemia there is no mucus, the pepsin is diminished or absent, and the pH is fixed.

It is suggested that the 'intrinsic factor of Castle' must be a product of gastric secretion which fails in the majority of cases when and as pepsin fails. Those few patients who secreted some ferment required less liver dosage than those who had no pepsin in their secretion after stimulation.

The deposit of squamous cells obtained in the gastric secretion of cases of primary anaemia signifies the complete inability of that secretion to digest the cells that normally are shed from the oesophagus and are carried down into the stomach.

By examinations of the gastric secretion without the introduction of any diluent it is possible to grade the degree of gastric failure. The stages have been detailed—cases of secondary anaemia falling into the second and third stage while those of primary anaemia fall into the fourth and final stage.

The patients investigated in this paper were all under the care of the Honorary Physicians of the Middlesex Hospital, to whom the writer is indebted for their kind permission in allowing these observations to be made. The writer also wishes to thank Dr. Izod Bennett for his helpful criticism; Professor James McIntosh, Dr. R. W. Scarff and Dr. Lionel Whitby for much helpful

advice; and lastly, to Professor E. C. Dodds for granting all facilities at the Courtauld Institute of Biochemistry for the investigations on the gastric secretions.

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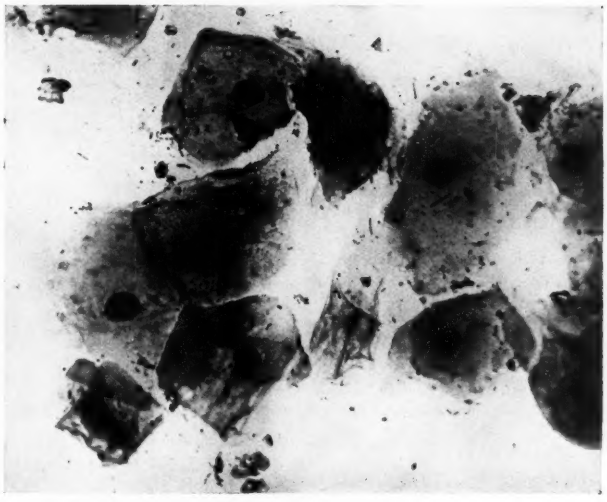

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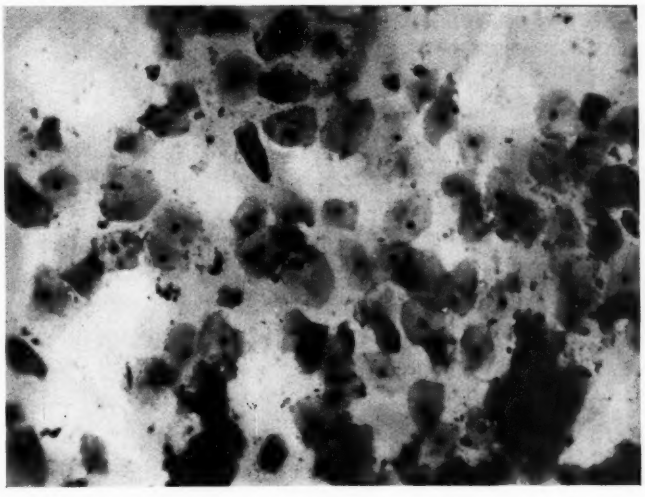

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Deposit from Gastric Juice in Pernicious Anaemia

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THE ELIMINATION OF FOCAL SEPSIS IN THE TREATMENT OF PARATHYROID TETANY[1]

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(From the Medical Professorial Unit, St. Bartholomew's Hospital)

In consequence of the irregular distribution of parathyroid tissue in man, tetany occurs from time to time as a sequel to removal of large portions of the thyroid gland; and the impossibility of assuring that sufficient parathyroid tissue is left makes the occurrence of such accidents inevitable. Such tetany may appear shortly after the operation, be severe and dangerous, and require vigorous treatment, but after a few days disappear; it is then assumed that a large part of the parathyroid tissue has been removed, but that the remainder, after the operative disturbance has subsided, is able to provide for the requirements of the body. The condition may be permanent; it then seems likely, either that no parathyroid tissue was left, or else that the portions remaining have atropied from overwork, sepsis, or implication in scar tissue, or at least have failed to hypertrophy.

The treatment of these permanent cases is difficult, even with the aid of physiologically active parathyroid extracts, and initial success may be followed by ultimate failure (1). The effect of parathyroid extract in raising the serum calcium excretion may be absent or soon be lost in comparatively normal individuals, but its action in depressing the serum inorganic phosphorus may persist (1, 2).

The two cases reported illustrate the difficulties in treatment with parathyroid extracts and the value of other methods, particularly the importance of the removal of chronic sepsis.

Case 1. Mrs. X., aged 48, was admitted to hospital on October 29, 1926. As a child she had not been strong and had been subject to bilious attacks, but in adolescence her health improved, and she became able to lead the life of a hospital nurse. She was married at the age of 30, and had one child born a year later. In 1921 she had an illness of which the features were vomiting, hiccough, sleepiness, and severe pain in the teeth; this was diagnosed as encephalitis lethargica. The illness passed without interval into Graves' disease, characterized by goitre, tremor, loss of weight, and auricular fibrillation. In January, 1926, there was an attack of pyelitis. Thyroidectomies were performed by Mr. T. P. Dunhill on the 1st and 17th of June 1926, and were followed by great improvement, a gain of 17 lb. in weight, and a return to normal cardiac rhythm. On June 22, five days after the second thyroidectomy, she developed

[1] Received May 7, 1931.

laryngeal stridor, loss of voice, cramps and contractures of the hands, and inability to see to read. The attack lasted for one hour, and was followed by similar attacks which occurred almost daily. After an acute tonsillar infection on September 3, the attacks, particularly the stridor, became much more severe. On three occasions she had epileptiform seizures in which consciousness was lost without warning, the tongue was bitten, and the urine passed.

When first seen by us she was constantly grinning, at times flushing, and continually pulling her fingers, saying that they were stiff. At times the fingers flexed and adducted involuntarily. Chvostek's and Trousseau's signs were present. She was a pale, well-built woman. The teeth had all been extracted.

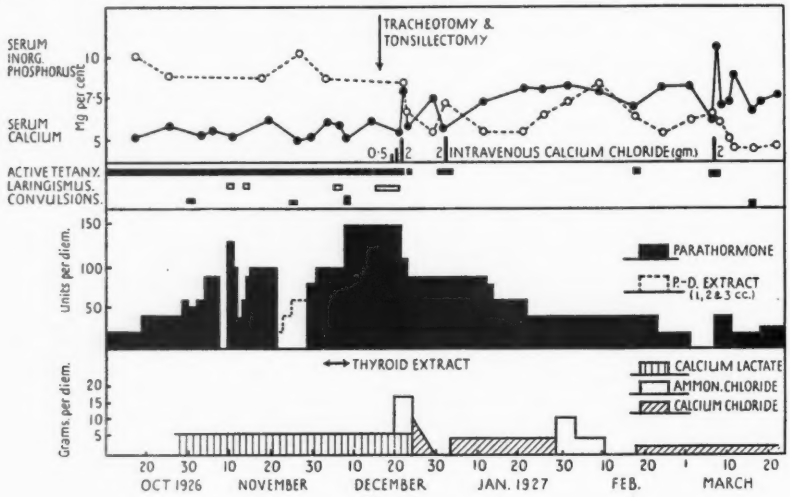

FIG. 1.

The tonsils were large, fibrous and septic, and the tonsillar glands were enlarged but not painful. The neck showed the scar of the operation, and there was no palpable thyroid. The apex beat was in the fifth intercostal space 5½ inches from the mid-line, and the heart sounds were clear and regular. Blood pressure, 130/98. The abdomen and legs showed no abnormality. Urine (catheter): opalescent, acid, trace of protein, many pus cells, and *B. coli*. No X-ray or other evidence of calculus. Standard metabolism + 20 per cent. After 24 hours without treatment the serum calcium was 5·05 mg. per cent.; inorganic phosphorus 10·2 mg. per cent.; pH 7·45, and CO_2 content 69 volumes per cent. The blood urea was 23, uric acid 3·6, creatinin 1·5, and creatin 4·9 mg. per cent.

Course and Treatment. Before admission the following treatment was given: calcium lactate, 2 grm., three times daily; parathormone (Collip) up to 20 units daily; dried thyroid 0·12 grm., and six drops of Lugol's solution daily; and potassium bromide since the last seizure.

The course of the illness, the treatment, and the changes in blood chemistry during her stay in hospital are recorded in Fig. 1. On admission, the calcium lactate was continued, and the parathormone increased to 20 units twice daily. After an epileptiform convulsion two days later, the parathormone was increased to 50, and then to 90 units, but this was without any clear effect on her symptoms, or on the serum calcium. The supply of parathormone then failed, and for two days saline injections were given as a psychological control; severe spasms and laryngismus followed. On 100 units she was a little better, but experienced another attack of laryngismus. Through the courtesy of Dr. Dickens and Professor Dodds we were able to try the effect of a parathyroid extract

prepared according to their directions (3) by Parke Davis & Co.: it appeared to be equally ineffective at the dosage suggested, and after a four days' trial the serum calcium had fallen below 5, and another epileptiform attack occurred. In spite of great disappointment at the results of these parathyroid preparations, we were of the opinion that some small degree of benefit had accrued from the Collip product, and, as this was again available, it was decided to return to it. A period of greater comfort ended in a severe laryngeal spasm (December 6); the preceding day had been foggy, and dry thyroid, 0·6 grm., had been added to the treatment three days before. The thyroid which had been reduced was omitted. Luminal, 0·12 grm., was given daily.

The attacks of generalized convulsions and of laryngeal spasm with asphyxiation were very impressive, and it was felt that drastic measures should be adopted to prevent them. The parathormone was raised to 150 units, and, on December 14, the tonsils were removed after a preliminary tracheotomy. The tonsils were enlarged, fibrous, and contained thick pus in which a haemolytic coliform bacillus predominated. The operation was followed by very severe tetany and laryngismus, which were partially relieved by chloral hydrate. Fifty cubic centimetres of a 1 per cent. solution of calcium chloride administered intravenously had no effect; 50 c.c. of a 2 per cent. solution gave a few hours' relief; 50 c.c. of a 4 per cent. solution gave complete relief for 24 hours, at the end of which the serum calcium, which had risen to 8 mg. 90 minutes after the injection, had fallen to 6 mg. per cent.

Ammonium and calcium chlorides were then given by the mouth with the object of producing an acidosis (4, 5), which is recognized to be effective in the treatment of tetany (6). Owing to difficulties in supply, the parathormone was reduced to 90 units. The tetany improved strikingly. These drugs caused anorexia and vomiting, but the patient welcomed this as an alternative to the tetany. Calcium chloride appeared to cause a rise in serum calcium to 7·7 mg., and a fall in phosphorus to 5·6 mg. per cent., while the CO_2 was reduced to 55 volumes per cent. without change in pH. Gastric intolerance necessitated the replacement of the calcium chloride by a litre of milk; this change was soon followed by definite tetany, a fall in calcium, and a rise in phosphorus. In a few days she was able to take 1·5 grm. of calcium chloride in cachets four times daily. In the middle of January, the throat was healed, and the urine had become sterile; the serum calcium was over 8 mg. per cent., and the phosphorus under 6 mg. per cent. The parathormone was reduced to 40 units without ill effect. Ammonium chloride was substituted for calcium chloride successfully, but withdrawal of the former was followed after some days by a return of the tetanic symptoms and a fall in serum calcium. Calcium chloride was recommenced. As there had been no attack of laryngismus for two months the tracheotomy tube was removed (February 24).

At the end of February the parathormone was reduced to 20 units. After eight days the serum calcium had not fallen. The parathormone was then omitted. Five days later there were definite carpo-pedal spasms, and the calcium had fallen by 2 mg. per cent. Two grammes of calcium chloride were given intravenously, and the parathormone was recommenced (40 units). A second attempt to reduce the parathormone resulted in severe generalized convulsions with a low blood calcium; the form which this attack of tetany took may have been influenced by omission of the luminal during the preceding fourteen days. She returned home at the end of March, taking 35 units of parathormone daily in two doses, 4 grm. of calcium chloride a day in cachets, and 0·12 grm. of luminal at night. Parathyroid grafts had been inserted in October and November, but no evidence of their activity followed.

At home she improved steadily and became able to lead an active social life, and the subsequent progress is summarized in the table. The serum calcium remained between 8 and 9 mg. per cent.

Summary of Changes after leaving Hospital (Case 1)

Date.	Serum Calcium. mg. %.	Serum Inorganic Phosphorus. mg. %.	Serum CO_2 Content. vol. %.	Treatment.	Result.
5.5.27	8·8	4·8	57	Parathormone 20. 15 units. $CaCl_2$ 4 grm. Luminal 60 mg.	No tetany
23.6.27	8·5	6·3	63	No change	No tetany
12.10.27	8·1	—	—	No change	No tetany
18.11.27	9·5	5·0	54	Parathormone stopped to-day. $CaCl_2$ 8 grm. Luminal 60 mg.	No tetany
21.11.27	9·8	5·3	—	No change	No tetany
22.11.27	9·5	—	—	No change	No tetany
24.11.27	9·0	5·5	53	No change	No tetany
2.12.27	8·1	—	—	Parathormone restarted on 3rd. 20. 15 units. $CaCl_2$ 4 grm. Luminal 60 mg.	Tetany: carpo-pedal spasms
19.7.28	7·3	5·6	—	Luminal reduced to 30 mg.	No tetany
Jan., 1929	—	—	—	Parathormone reduced by steps to 20 units	No tetany
25.4.29	7·2	7·1	—	No change	No tetany
23.12.29	6·4	—	—	No change	No tetany

N.B.—By 'No tetany' is meant the absence of carpo-pedal spasms, laryngismus, visual disturbances, Chvostek's and Trousseau's signs.

In November 1927 she returned to hospital. The dose of calcium chloride was doubled, and the parathormone was stopped. The serum calcium fell from 9·8 to 9 mg. per cent. in three days, but the patient remained quite fit and insisted on returning home. A week after that she experienced carpo-pedal spasms, and the calcium had fallen to 8 mg. In the following week further spasms occurred. The parathormone was recommenced, and the calcium chloride reduced to the lower level. During 1928 she remained very well, although there was occasionally tingling or cramp at night. The serum calcium was lower at 7·3 mg. per cent. In the latter part of that year the parathormone treatment was altered to a single injection of 35 units, and the dose was then reduced, by 2 units at a time, to 20 units. In April 1929 she reported that after three months on this dose she was just as well; the serum was 7·2 mg. per cent.; the blood urea was 30 mg. per cent. X-ray examination of the bones at this time showed normal calcification. In December 1929, on the same treatment, the serum calcium was 6·4 mg. per cent., and there had been no return of symptoms; and in July 1930 she was reported to be leading an active social life with no disability apart from occasional cramp when tired.

Case 2. B. B., aged 20, was admitted to hospital on April 29, 1929. She had been well until four years previously, when she fell ill with acute appendicitis. The appendix was removed; pneumonia followed the operation. From that time the patient was never again in robust health. A year later she noticed a swelling of her neck, and shortly afterwards began to find difficulty in swallowing. Two years before she first came under our observation the right lobe of her thyroid was removed in a hospital near her home. This operation did not relieve her symptoms, and a second was carried out eight months later, at which the left lobe of the thyroid was removed. Two days after this second operation a new series of symptoms appeared. She had a tingling sensation spreading from her head to her toes. Her hands and feet became numb and her fingers and toes stiff, so that she could not move them freely. She began to have attacks of difficulty in breathing. Swallowing was often uncomfortable. These symptoms persisted, though with varying intensity, during the sixteen months before she came into hospital.

The patient was a well set up young woman. She was not anaemic, nor did her appearance suggest that she had any chronic infection, She was sluggish mentally, and she resented the discipline of hospital life. The scar of the operation-wound on her neck had undergone some keloid degeneration. Centrally in the neck there was a small palpable lump which was thought to be the isthmus of the thyroid gland. Her fingers and toes were stiff, and, for long periods together, fully developed carpo-pedal spasm could be observed.

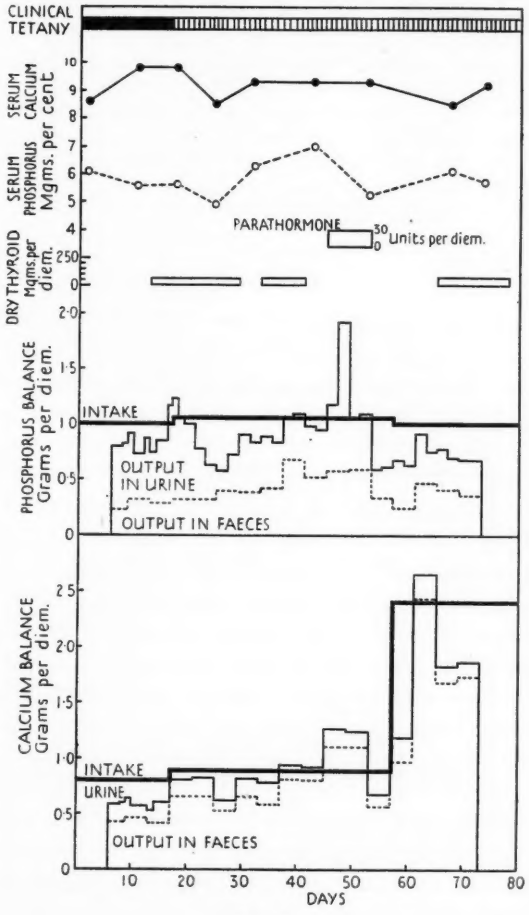

FIG. 2.

Chvostek's sign was constantly present. At intervals, more especially at night, she had difficulty in breathing, apparently arising from laryngeal spasm. Physical examination revealed no other defects. Her condition was thought to be due to myxoedema and tetany resulting from the removal of the greater part of her thyroid and parathyroid tissues. The standard metabolism could not be measured with certainty, because of her mental attitude. Such readings as were obtained did not depart from the normal (23/5/29, + 24 per cent.; 27/5/29, + 18 per cent.; 10/6/29, + 11 per cent.). There was in the blood-serum 8·6 mg. per cent. of calcium and 6·1 mg. per cent. of inorganic phosphorus.

The measurements of the minimal currents to produce contraction of the flexor muscles of the wrist were: cathodal closing, 3 milliamperes; and anodal closing, 3·5 milliamperes.

Various attempts were made to relieve the patient's symptoms (Fig. 2). While these were in progress, the serum calcium and phosphorus were estimated from time to time, and the excretion of calcium in the urine and stools was measured, the diet being kept constant. Luminal 0·12 grm., dry thyroid

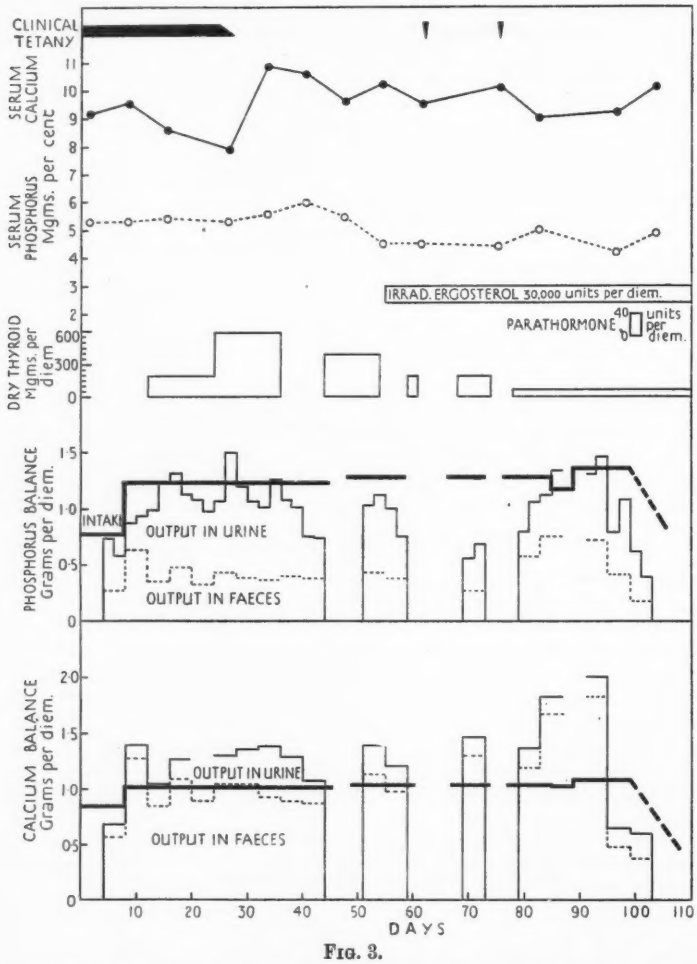

FIG. 3.

0·6 grm., Collip's parathormone 30 units, and calcium lactate 4 grm. were given daily, singly and in various combinations. None of these drugs materially altered the patient's condition. The calcium and phosphorus metabolism was unaffected; the symptoms varied in degree, but it was impossible to believe that improvement, when it occurred, had any relation to the treatment. On July 12, 1929, she went home in very much the same condition as when she was first seen. She was readmitted on November 7, 1929, still with the same symptoms, and the observations were continued. On this admission (Fig. 3) she was given increasingly large doses of dry thyroid, 0·2 grm. a day for

twelve days, followed by 0·6 grm. a day for another twelve days. At the end of that time the patient showed some signs of overdosage, such as tachycardia, sweating, and restlessness, but the carpo-pedal spasm and all signs of tetany, except the irritability of the facial nerve, had disappeared. This change was accompanied by a rise in the serum calcium from 7·9 mg. per cent. on December 2 to 10·8 mg. per cent. on December 9. Although the calcium returned later towards its former level, the symptoms of tetany did not come on again. Dry thyroid, first 0·4 grm. a day, and then 0·2 grm. a day, was given, except at such times as signs of overdosage were present.

On January 6, 1930, the patient fell ill with acute follicular tonsillitis, and with the illness all the signs and symptoms of tetany returned. The serum calcium did not fall below its usual level. The sore throat improved very rapidly, and with its disappearance the tetany abated. The tonsillitis recurred on January 20, with the same recrudescence of the tetany, but again without any notable fall in the serum calcium. On February 20, 1930, the patient's tonsils were removed; on February 25 she went home, taking 0·2 grm. of dry thyroid a day, and free from any symptoms of tetany.

Discussion.

Every case of tetany has its own peculiar features and difficulties, but we believe that the experiences of these patients present points of general application. It appeared that a very small amount of parathyroid survived the operation. The subsequent course was largely influenced by sepsis in the tonsils and urinary tract, which made extra demands on the parathyroids and hindered hyperplasia of any remnants. The relation between infections and thyroid dysfunction has been emphasized by Cole and Womack (7), and the increased insulin requirements of diabetics who become infected has been demonstrated by Graham (8). We suggest a similar influence of infection in parathyroid deficiency, and in Case 1 would explain in this way the increasing severity of the tetany in the six months between the thyroidectomy and the tonsillectomy, and the failure of massive doses of parathyroid extracts to develop their full biochemical response, or to do more than slightly mitigate the symptoms. In spite of this very discouraging result we were definitely of the opinion that, even at that time, some benefit did accrue from parathyroid therapy in this case. It was on these grounds that it was decided to remove the tonsils, which were regarded as of importance, both as a reflex factor producing laryngismus, and as a source of sepsis, aggravating the pyelitis and possibly creating further endocrine disturbance.

The production of an alimentary acidosis with ammonium and calcium chlorides was a most effective measure in the first case. The prompt return of the tetany when it became necessary to omit them in December, and the abrupt fall in serum calcium, showed that the greater part of the relief then obtained was due to the calcium chloride and little to the parathyroid. After their omission in February, symptoms developed only after some days and were very much milder. From the change in response it appeared that on the second occasion the natural parathyroid secretion and the smaller parathyroid injection were playing a more substantial part. It has been our experience, and we

believe a general one, that for a considerable time after an operation for the removal of sepsis diabetics require more insulin, and that any ultimate benefit comes after the lapse of some weeks. A similar sequence of events is suggested in this case. The omission of a small dose of parathormone in March was the occasion for the rapid decline of the serum calcium and for a return of carpopedal spasms. No such convincing evidence of the activity of parathormone was obtained before the tonsillectomy, when far larger doses were being given. Calcium chloride was being given on the second occasion and calcium lactate on the first, but it would be difficult to attribute the difference in response to this. The large part which tonsillectomy played in relieving this patient from tetany and from dangerous laryngeal spasm is a point in favour of a tonsillectomy, if required, being performed before a thyroidectomy.

Salvesen (9) described the gradual readjustment of the body to a reduced level of the serum calcium, and Fisher and Larson (10) found that a low serum calcium following the control of acute experimental parathyroid tetany did not indicate impending active tetanic phenomena. Fortified by these reports, we persisted in the reduction of parathormone in 1928 and 1929 in the face of a low serum calcium; this course was justified by the patient's remaining very well. It is possible that by that time the patient was losing her response to parathormone. That this was so, is suggested by the following considerations. In July 1928 the serum calcium was 2 mg. per cent. lower than it had been seven months before on the same dose of parathormone, but the inorganic phosphorus had not risen; after the subsequent reduction of parathormone the calcium fell no further, but the phosphorus rose 1·5 mg. per cent. This sequence of events would agree with Aub's (1) findings that parathormone may retain some effect on the phosphorus after it has lost its action on the calcium. The serum inorganic phosphorus was notably high. A rise to 6 or 7 mg. per cent. is usual in parathyroidectomized animals (9, 11, 12), but it has been found as high as 12 mg. per cent. (11). The lower figures have been recorded in man (12). Before ammonium chloride was given in this case it varied from 10·8 to 9·0, the lower figures corresponding to periods of higher dosage of parathormone; this action of parathormone in reducing the serum phosphorus was just perceptible, and is comparable to the minimal rise of calcium produced at the same time. Such a high level of phosphorus tends to increase the liability to tetany by decreasing the ionization of calcium (13), and the definite lowering of this level by calcium and ammonium chlorides (14, 15) was an important factor in their successful action.

Mirvish and Bosman (16) found that ovarian extracts produce a slow prolonged fall of the serum calcium. The clinical application of this work to tetany remains to be shown, but in this case, and in others, which we have reported (17), prolonged amenorrhoea has pointed to depression rather than to exaltation of ovarian activity.

Two grammes of calcium chloride intravenously were effective in abolishing all tetanic manifestations for almost a day; smaller doses were useless. Should

this salt enter the tissues around the vein it causes a severe reaction, even sloughing; more serious is the rare occurrence of sino-auricular block, and of respiratory paralysis (18). Intravenous calcium should be reserved for emergencies, and should always be given slowly and in dilute solution. That calcium chloride by the mouth has an appreciable effect in raising the total serum calcium was shown when it was withdrawn on December 29, 1926. The lactate is probably less effective (19, 20). The chief effect of the chloride is to increase the calcium ionization by producing an acidosis and reducing the serum phosphorus (5, 6, 13, 14, 15).

In the second case the conditions were a little different. This patient had been deprived not only of sufficient parathyroid tissue to meet her ordinary needs, but she seemed also to suffer from lack of thyroid secretion. Luminal, in the doses she was given, brought no relief. Parathormone had no effect in raising the serum calcium or in modifying the tetany, even though the quantity given was sufficient to alter the calcium and phosphorus metabolism so that their excretion was greater than the intake. Only after toxic doses of dry thyroid were given did the symptoms change. This relief was accompanied by no dramatic rise in the serum calcium. The impression was formed that the thyroid produced its effect by increasing in some way the availability of the calcium in the serum rather than by increasing its total quantity. Hjort and Eder (21) have described their observations on a patient whom they treated for tetany complicated by hypothyroidism. They found, as we have, that parathormone given alone had little effect either in raising the serum calcium or in the relief of symptoms. When it was given in conjunction with dry thyroid, 0·7 grm. daily, the serum calcium rose and the symptoms were relieved. The authors suggest tentatively that the 'thyroid medication assisted in making available calcium stores which resisted ordinary parathyroid treatment'. They regard the action of the thyroid as an adjuvant to that of the parathormone. Our own experience in the case reported here leads us to think that it was the thyroid which produced the change in the symptoms, and that this effect is independent of the administration of parathormone. Aub and others (22) have shown that in cases of Graves' disease there is a loss of calcium and phosphorus from the body which, in the course of time, results in a considerable degree of decalcification of bone. It is not unreasonable to suppose that thyroid given in sufficient quantities by the mouth would produce similar results. Yet in the case reported, there was no great rise of calcium in the blood, nor were the calcium and phosphorus intake and excretion ratios materially altered by the dose, 0·6 grm. a day, which was being given when the tetany stopped. Accordingly, it is believed that the improvement was effected by altering the quality rather than the quantity of the circulating calcium.

Whatever the mechanism of recovery, it was not effective in protecting the patient against intercurrent infection. When she developed follicular tonsillitis, her tetany returned, and when the tonsillitis cleared up the tetany improved. In this case it is improbable that the tonsillitis had a prolonged

effect on the condition. On both admissions her tonsils were subjected to a scrutiny which our previous experience made very exacting; each time they were considered above suspicion. The tonsillar infection which brought about the return of her symptoms was truly intercurrent. A carbuncle, or an attack of influenza, would probably have had the same result. The tonsils were removed in the end to eliminate, at any rate, this particular kind of accidental setback.

Summary.

1. Two cases are described, in which persistent tetany followed thyroidectomy.

2. Observations on the calcium and phosphorus metabolism in these cases are recorded.

3. The effect of treatment in various forms on the symptoms, and on the calcium and phosphorus metabolism, is described. Relief of symptoms in one case was eventually obtained by giving parathormone; in the other, dry thyroid gave relief while parathormone failed.

4. Focal sepsis is shown to be an important factor in increasing the severity of the condition, and in preventing its successful treatment.

The writers wish to express their thanks to the Medical Research Council for a grant to one of them (G. C. L.).

Methods. The blood was taken at the same hour on each occasion. It was centrifuged immediately, and the serum taken for the phosphorus determination. The methods used for the quantitative determinations were: calcium, Clark and Collip (23); inorganic phosphorus, Benedict and Theis (24), and Fiske and Subbarow (27); pH, Hastings and Sendroy (25); and CO_2, Van Slyke and Neill (26).

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616.12—008.313

RIGHT BUNDLE-BRANCH BLOCK[1]

AN ANALYSIS OF THE CLINICAL RECORDS OF FIFTY-SIX CASES WITH TYPICAL ELECTROCARDIOGRAMS

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With Plates 23, 24

The investigation of this series of fifty-six cases was undertaken with the object of reviewing the signs and symptoms associated with the condition, and of obtaining figures which might prove useful for prognosis. We have adhered throughout to the criteria laid down by Lewis (1) and others for selection of curves which we have included in the present group, namely:

1. That the Q R S interval should exceed 0·1 second.
2. That the Q R S deflexion should show a considerable amplitude.
3. That, in these exaggerated complexes, the Q R S deflexion should be notched; and
4. That the T wave should be large, and opposite in direction to the main Q R S deflexion

These alterations in the Q R S complex are explained by Lutembacher (2) as follows:

'After destruction of the right bundle there is not hemi-systole, but retarded contraction of the right ventricle. The retardation is due to the fact that the speed of conduction in the myocardium is only 300 mm. per second as compared with 5,000 mm. per second in the bundle.

After destruction of the right branch the left ventricular effect alone is present. During the first phase the record is purely a levo-cardiogram. It is only then slowly, after about 0·04 second that the excitation reaching the right ventricle through an aberrant path, produces its effect. This right ventricular effect appears when it intervenes a little after the principal summit, which it either increases, or it may interrupt the line of descent by a little notch.

This retarding effect of the right ventricle makes the line of descent less vertical. As a result the angle, which is normally narrow, has an enlarged base, and the duration of the Q R S complex is augmented to more than 0·1 second.'

Willius (3) has recorded a series of 105 cases, 99 of these being due to lesions of the right bundle, and the remaining 6 to lesions of the left bundle. In Cowan and Bramwell's (4) series of 24 cases, only one was recorded as

[1] Received February 13, 1931.

involving the left bundle. In our series of 56 cases, the right bundle was involved in every instance.

The explanation of this predominance of right bundle-branch lesions as compared with left may possibly be found when the blood supply of the two bundle-branches is compared. The right limb of the bundle is mainly supplied by the septal branches of the anterior descending branch of the left coronary—the artery most usually affected in coronary disease. One of these branches accompanies it in the vestigial moderator band. The right coronary may supply twigs through the Ramus septi fibrosi and Ramus cristae supraventricularis. The left limb receives blood from the septal branches of both coronary arteries.

The rarity of left bundle lesions may be accounted for by the diffuse anastomosing supply it receives from the septal branches of both coronary arteries. Radiograms (5) of the injected coronary circulation have demonstrated the numerous anastomotic connexions of the vessels to the neuromuscular tissue, and show that this tissue is especially well protected in most cases of coronary disease.

Of the 56 cases investigated, 30 were patients attending the Royal Victoria Hospital, Belfast, and 26 were patients who had been seen in consulting practice. The incidence was roughly 1 per cent. in each of the series of 3,000 hospital cases, and 2,500 private cases. It is perhaps of interest to note, for the sake of comparison, that among 3,000 men of military age in France admitted to hospital as cases of D.A.H. and V.D.H., there was only one case of bundle-branch lesion (6).

Our series has lent further support to the view that the condition of bundle-branch lesion tends to be permanent when once established, as in no case did we find intermittency. Cowan and Bramwell (4) have only recorded one exception to this rule; but three other cases of temporary branch block are mentioned by them, one of Lewis's in which the temporary block was found during a febrile attack, one of Ritchie's occurring during an attack of jaundice, and one of Hewlett's occurring in a case of urinary sepsis. Willius and Keith (7) report three cases where the block was intermittent, disappearing for some time to return again.

Experimental support to the view that such cases are due to temporary toxic conditions is given by Daniélopolu (8) and Danulesco (9), who have demonstrated that, by stimulation of the vagus, more especially after injections of adrenalin or atropin, irregularities of conduction in the ventricles may be shown if the patient has previously suffered from some intercurrent disease. They have only been able to produce these effects in one healthy subject.

An investigation of the aetiological factors in our series showed that previous rheumatic infection could only be definitely traced in 9 cases; syphilis in 3 cases; bacterial endocarditis in 2 cases (one of these being apparently associated with coronary thrombosis); influenza (of recent origin) in 7 cases, and acute fevers (such as typhoid and scarlet fever) in 7 cases also.

Among other conditions present we found the following: severe secondary anaemia in 5 cases; bronchitis and asthma in 5 cases; nephritis in 4 cases, and each of the following in 1 case only—goitre, gout, and 'strain'. There was no history of any previous illness in 10 of the cases.

Thirty-six of the cases analysed were men, and the remaining 20 were women. The average age incidence in the hospital series was 58·6 years, and in the series of private cases 63·1 years. In the combined series 2 cases were in the eighth decade, 10 in the seventh, 18 in the sixth, 17 in the fifth, and 9 in the fourth. These figures refer to the age at which the patient was first examined.

The symptoms and signs are practically those commonly found as indicative of myocardial degeneration; thus dyspnoea on exertion was complained of in 43 cases; and effort pain in 22 cases. A more marked degree of myocardial insufficiency was present in 34 cases.

Other findings were: palpitation (16 cases), general weakness (10 cases), insomnia (6 cases), gastro-intestinal symptoms (5 cases), vertigo (1 case), and syncope (1 case). One case did not complain of any cardiac symptoms.

A noteworthy finding, and one probably associated with the higher case mortality in the hospital series, was that oedema was present in 13 cases of this group; and in only 2 of the non-hospital group.

Cardiac enlargement was present in almost all cases; and there was very pronounced enlargement of the heart in 10 cases.

Evidence of mitral disease was found in 34 cases, and of aortic disease in 8 cases.

Two cases only showed the presence of pericardial friction. Bacterial endocarditis, as previously noted, was present in 2 cases.

Triple rhythm, which has been mentioned as an evidence of bundle-branch lesion, was only observed in 7 cases. Of other cardiac arrhythmias, auricular fibrillation was noted in 4 cases; pulsus alternans in 1 case, and extra systoles in 1 case.

Arterio-sclerosis, as determined by the condition of the radial artery, in moderate or advanced degree, was found in 14 cases. Twenty-six patients showed a systolic blood-pressure of over 150 mm., and in three the reading was over 200 mm.

Albuminuria was recorded in 14 of the hospital cases, as contrasted with only 4 of the non-hospital series.

It was only in the most recent cases examined that an X-ray of the heart was taken, and this always with the tube at about twenty-eight inches from the plate, and the patient standing with his back to the tube. These pictures, of course, suffer from the defect of parallax, but have been taken more or less constantly in the same relative position. Compared with many other myocardial conditions the outline has been somewhat of the 'Baby Boot' type of shadow, that is to say, rather wide at the aortic junction, and a shadow preponderating very much towards the left.

Prognosis. The case mortality in the two groups of cases was as follows: In the hospital group (30 cases) seven patients were alive, nineteen were dead, and four could not be traced. This showed a case mortality of 73 per cent. of traced cases.

The second, or non-hospital group (though the average age was higher) showed a case mortality of 42 per cent.; fifteen patients out of twenty-six being still alive.

In the 30 cases in which death has occurred it is interesting to record, first, the period elapsing between the onset of symptoms and the electrocardiographic diagnosis; and, secondly, the interval between this diagnosis and the death of the patient.

Tables I and II appended show these facts in detail, and institute a comparison between the first and second series.

TABLE I.

Time ill before examination.	Hospital.	Other cases.
3 months or under	6	0
3–6 months	3	2
6–12 months	5	6
1–2 years	0	1
2–3 years	1	2
3–4 years	1	0
5–6 years	1	0
Not stated	2	0
	19	11

TABLE II.

Time from Electrocardiographic diagnosis till death.	Hospital.	Other cases.
3 months or under	5	3
3–6 months	2	1
6–12 months	4	2
1–2 years	3	4
2–3 years	0	0
3–4 years	1	1
5–6 years	2	0
Not stated	2	0
	19	11

Of the series of cases recorded by Willius, 27 per cent. were still alive, two of these having survived for six years after the diagnosis of bundle-branch block was made.

Cowan and Bramwell record 1 case alive for four years, and 2 cases alive for three years.

In our series 22 cases (39·3 per cent.) are still living. Of these no fewer than four have been alive for nine years since the electrocardiographic diagnosis was made.

One case is of thirteen years' duration, 1 of seven years', 3 of three years' 1 of two years', 3 of eighteen months, 4 of one year, and 5 of a period under one year.

These electrocardiograms are illustrative of the case mentioned in the text, in whom right bundle-branch block has persisted for thirteen years. During this period he has had several severe attacks of cholecystitis and of influenza, once complicated by pneumonia. Notwithstanding his age, he is still able to take an active interest in his profession.

Carter (10) also finds that 'an organic lesion confined to one branch of the A–V bundle is hardly one which can be regarded as jeopardizing life. We find that a bundle-branch lesion may be present for many years, and the heart still show general efficiency'.

(This paper, which was read at the meeting of the Association of Physicians in Belfast in 1927, was undertaken under the direction of the late Professor J. E. MacIlwaine. It was later subjected to revision by him; and its publication has been delayed owing to his prolonged illness and death.

We are indebted to Dr. John S. Campbell and Professor Walmsley for the preparation of the photograph showing the blood-supply to the right branch of the A–V bundle.)

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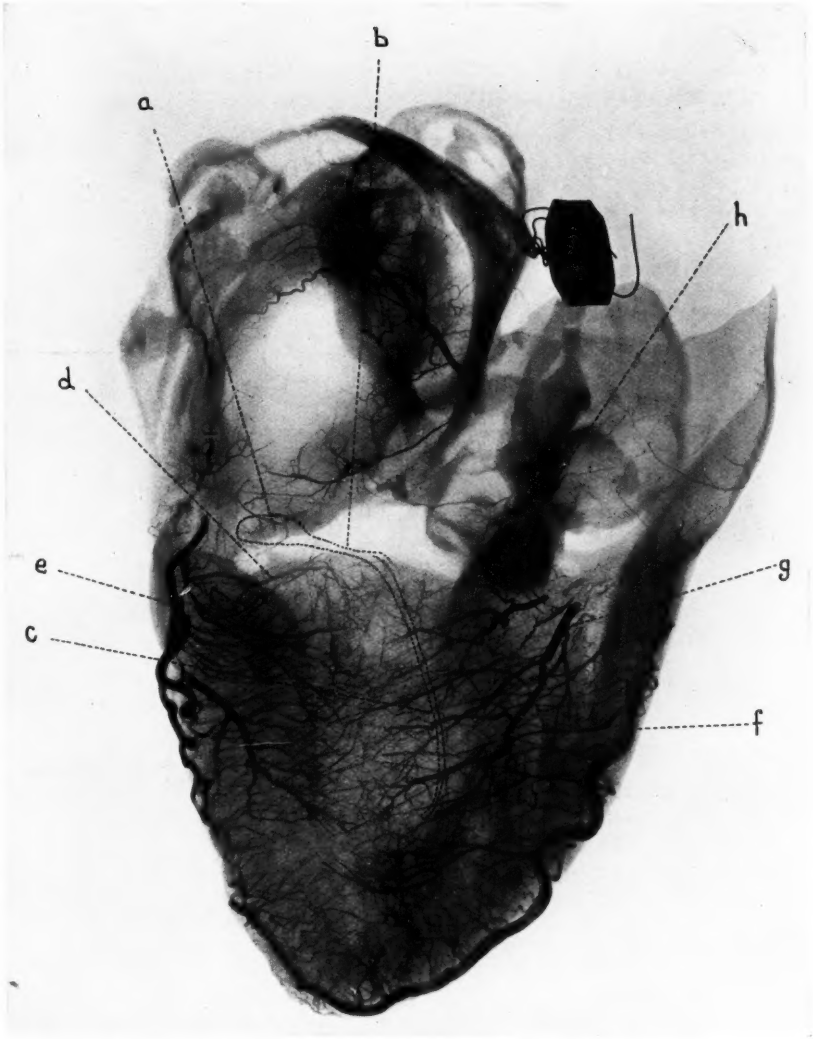

Injected heart, showing blood supply to the right branch of the bundle.
By John S. Campbell

a. A.V. node. *b*. Main stem of bundle. *c*. Right bundle-branch.
d. Ramus septi fibrosi. *e*. Post. descending branch right coronary.
f. Ant. descending branch left coronary. *g*. Septal branches of (*f*).
h. Right coronary.

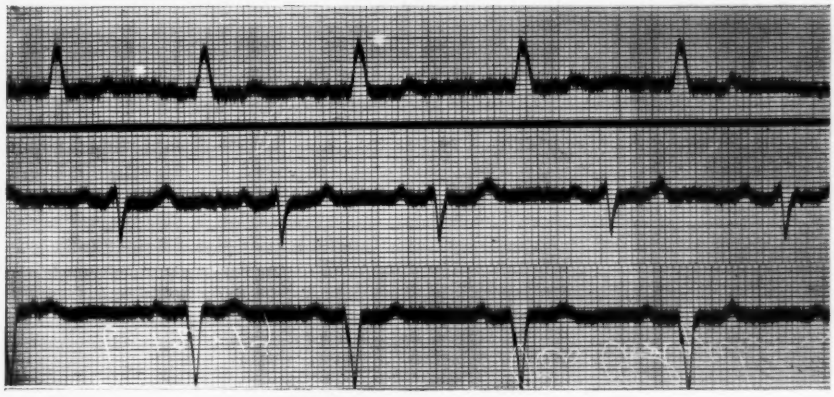

FIG. 1. Male aet. 66

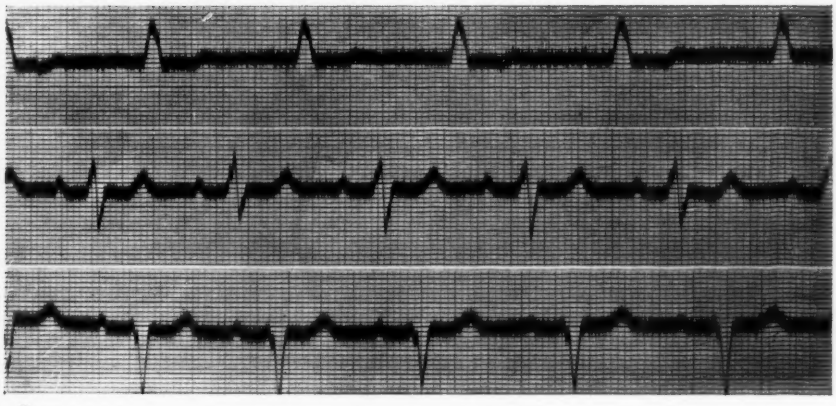

FIG. 2. Same case, aet. 79

616.912.5

THE CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF VARIOLA MINOR AND ITS DIFFERENTIAL DIAGNOSIS[1]

By CHRIS. J. McSWEENEY

Introductory Note.

During the last eight years a type of smallpox has been prevalent in England and Wales which in its clinical and epidemiological behaviour differs materially from the disease as usually described in medical textbooks.

Although this different type has not so far obtained a foothold in the city of Cardiff, the writer has had an opportunity of studying several hundreds of cases, first in 1927 when detailed to act as temporary Medical Officer of Health in a neighbouring town where an epidemic of smallpox had assumed alarming proportions, and in succeeding years when cases from many of the infected areas in Monmouthshire and Glamorgan were accommodated in the Cardiff Smallpox Hospitals. The description of the disease here given is based on these experiences.

The two outstanding features of this variety of smallpox have been mildness of the accompanying symptoms and a relatively slight degree of infectivity. Various titles have been bestowed on the disease, e.g., 'alastrim', 'modern smallpox', 'varioloid', &c., but most of these are open to objection on the grounds of inaccuracy. Indeed, the continued use in medical literature of the term 'alastrim', implying, as it does, a clinical entity distinct from smallpox, can no longer be justified in the light of recent experimental work. Blaxall (1) has shown that identical lesions are produced in monkeys by inoculating material obtained from cases of alastrim on the one hand and smallpox on the other, and he has further demonstrated that the virus obtained from cases of alastrim produces an immunity to vaccinia. Gordon (2), working with material obtained from Gloucester 'alastrim' and from virulent smallpox, could detect no difference in the serological behaviour of these viruses, both giving specific complement fixation and agglutination reactions with an anti-vaccinial serum. Ledingham (3), summing up his review of the immunological relationships of alastrim and smallpox, describes the prevailing type of smallpox as 'merely a variant of variola whose toxic properties for the human organism have become suppressed. . . .'

[1] Received February 21, 1931.

The term 'modern smallpox' is also misleading, for medical history shows that smallpox has varied in virulence from time to time and place to place. It is highly probable that the disease now prevalent in this country has existed for many decades in South and Central America under the title of 'alastrim', and in South Africa as 'Amaas'. Edward Jenner (4) himself, writing in 1798, mentions a Gloucestershire epidemic of smallpox which 'was of so mild a nature that a fatal instance was scarcely ever heard of' and he definitely described this disease as 'a variety of the smallpox'. In the history of smallpox, therefore, mildness of symptomatology is no new development, and although it has characterized most of the 60,000 cases of the disease which have occurred in England and Wales between 1922 and 1929, yet the Poplar Workhouse outbreak of 1922, the Hendon epidemic of 1927 and, more recently, the 'Tuscania' cases remind us that even in modern times smallpox of the appropriate strain, can be a very virulent and fatal disease.

The recent prevalence of the mild variety of smallpox and its negligible mortality, as contrasted with the lower incidence and higher mortality of the classical type in former years, is well shown in the following table which is taken from Sir George Newman's Annual Report for 1929.

	Year.	Cases.	Deaths.	Fatality per 1,000 cases.
	1911	295	23	77·97
	1912	123	9	73·17
	1913	115	10	86·96
	1914	64	4	62·50
	1915	90	13	144·44
	1916	149	16	107·38
	1917	7	3	428·57
	1918	63	2	31·75
	1919	294	24	81·63
	1920	263	30	114·07
	1921	315	5	15·87
Years of variola minor	1922	973	27	27·75
	1923	2,485	7	2·82
	1924	3,765	13	3·45
	1925	5,365	9	1·68
	1926	10,146	18	1·77
	1927	14,767	47	3·18
	1928	12,420	53	4·27
	1929	10,967	39	3·56

It is interesting to note that in this table for the first time in the statistics of the Ministry a distinction is made between the mild prevalent form (designated variola minor) and the classical virulent form.

In view of its continued prevalence it is regrettable that fuller accounts of variola minor have not, as yet, been included in standard medical works. The following description may, therefore, be of use to medical men confronted with the disease for the first time. In this review frequent reference to the classical type of smallpox is necessary for purposes of comparison. But while it is intended to emphasize those characteristics of the prevailing disease which do not conform to the 'classical' descriptions of smallpox, it will be obvious that the clinical resemblances of the two types and their common relation to vaccination furnish conclusive evidence that the milder disease is indeed small-

pox. It will be evident also that the distinction between the major and minor types cannot always be made with certainty as the result of a clinical examination. This difficulty is, of course, greatest when the disease makes its appearance for the first time in a district after an interval of freedom from infection. In such circumstances it will be wiser to treat the case as one of variola major until its course and, possibly, the behaviour of subsequent cases make it clear that the disease is of the minor type. The important matter for the medical practitioner is to recognize promptly the variolous nature of the milder disease, so that preventive measures may be taken without undue delay. The 'typing' in certain cases can only be done by the Public Health Department who are in a position to watch the evolution of successive cases and to obtain accurate information as to the origin and past history of the particular strain of smallpox in question.

I. *Clinical Characteristics of Variola Minor.*

Incubation period. The incubation period in the series of cases reviewed varied from ten to fifteen days. Instances where the incubation period exceeded fifteen days have been reported, but it is doubtful whether in these cases the operation of some unascertained source of infection, subsequent to the supposed source, can be entirely discounted. It is, however, quite certain that the incubation period of the minor type of smallpox may occasionally exceed by several days the maximum laid down for the classical disease. An incubation period of less than ten days was not encountered.

Period of invasion. The onset of the disease is sudden and is marked by headache, shivering, malaise, and pyrexia. These 'influenzal' symptoms are almost invariably present, but they are not always sufficiently severe to compel the patient to lie up. Backache is exceptional, and, if present, is never severer than the limb pains; and, indeed, the clinical picture is one of influenza, although prostration does not occur. The symptoms of invasion last at least forty-eight hours, but may continue for four, five, or even six days, the pyrexia meanwhile gradually subsiding. It is not an uncommon occurrence for miners and other workers to resume their occupation within three days of the onset of this disease. Prodromal rashes of any kind were not observed in a series of roughly 300 cases.

Period of eruption. The rash of variola minor never appears before the third day of the disease. It is commoner for the eruption to manifest itself on the fourth or fifth day, and it may be as late as the seventh or eighth day. In 166 consecutive cases where the accuracy of the history could be vouched for, the eruption appeared on the third day in 28, on the fourth day in 46, on the fifth day in 53, on the sixth day in 22, on the seventh day in 11, and on the eighth day in 6 cases. The rash first appears on the face, a few hours later it is present on the forearms and trunk, and within twelve hours is seen on the lower extremities. The eruption never comes out in crops, although in appearance

and development the lesions are usually found to be slightly more advanced on the face than on the extremities. The rash goes through the usual stages of evolution characteristic of classical smallpox, but maturation, though proceeding in an orderly fashion from papule to scab, is more rapid in the non-classical type. Secondary fever does not occur. *The appearance of the eruption in variola minor coincides with a cessation of all constitutional symptoms* and the patient at once feels much better and continues to improve daily, remaining free of pyrexia throughout. The papular stage lasts from thirty-six to forty-eight hours and by the fifth day the vesicles have usually commenced to pustulate. On the seventh or eighth day after the appearance of the eruption, scabbing will have commenced on the face, but it may be much later before the peripheral lesions begin to scab. In a few cases where the writer was able to see the rash of variola minor within twelve hours of its appearance, a small vesicle the size of a pin's head could be discerned embedded in the centre of the raised and rounded papule. The appearance of this early lesion was quite distinctive and quite unlike any lesion encountered in chicken-pox, but this appearance was not observed in several other early variolous rashes, where reliance had to be placed entirely on relative distribution, so closely did the papules resemble those of varicella.

The distribution of the eruption in the prevalent type of disease is essentially that of classical smallpox. The rash is centrifugally disposed, affecting the face and extremities rather than the trunk. It is more profuse on the face than on the upper extremities, and on the upper extremities than on the lower. The trunk very often shows lesions, but the rash is concentrated on the face and limbs. On the face the tendency for lesions to cluster around the nose, which is so characteristic of the classical type, is not so frequently observed. The lesions are never found in the orbits except in severe semi-confluent or confluent types. If the face is divided into three segments by imaginary lines drawn at the level of the eyebrows and the mouth, it is usual for the majority of the lesions to lie within the middle segment, but the departures from this rule are more frequent in variola minor than in variola major. On the limbs the centrifugal character of the eruption is as constant as in the classical type. An essential feature in the diagnosis of both types of variola is the relative distribution of the rash. Smallpox lesions may be found on any part of the limbs, but they are invariably more profuse distally. In a typical case of discrete smallpox the skin above the elbow will be found free, or almost free, of rash, but below the elbow the lesions are numerous and will be seen scattered along the tendon sheaths in the forearm and wrist, studded in the palmar area, and concealed between the contiguous borders of the fingers. On the thenar and hypothenar eminences (where the skin of manual workers tends to be thickened) the lesions tend to be deep-seated and approximate in character to those found on the soles of the feet. These lesions are felt rather than seen in the papular stage of the disease. It is always worth while looking or feeling for them, as they are quite diagnostic of variola. Lesions are rarely

found on the thigh in discrete cases, but clusters are frequently seen around the knee, particularly in miners who wear knee pads or straps, and in those women who do much scrubbing of floors. On the legs the constituents of the rash are found disposed along the flexor and extensor tendons at the sides and on the dorsum of the foot, around the malleoli and along the contiguous surfaces of the toes. The sole of the foot shows some lesions in a majority of all cases. Here the typical deep-seated pustule or 'seed' is most commonly seen in those portions of the foot subjected to most strain, viz., the heel and the ball of the toes. The arch of the foot usually escapes, but this feature is missing if the arch has been obliterated as in flat foot. The circular 'seeds' of smallpox lying in the deeper layers of the skin of the sole covered by shining epidermis are as characteristic of the non-classical as of the classical type of the disease.

When the trunk exhibits lesions, there are certain features of distribution which are commonly found in both types of smallpox. More lesions will be found on the back than on the chest and abdomen. At the back more lesions are found on the dorsal than on the lumbar and sacral regions. There is a similar gradation on the front of the body, more lesions being found on the chest than on the abdomen. There is, therefore, a diminution, progressively downward, in the number of lesions found on the trunk. A tendency towards centrifugal disposition is also frequently noticeable in the trunk lesions, the eruption shunning the midline of the body and aggregating over the scapular and hip regions. It is extremely rare to find smallpox lesions in the axillary spaces. In the present series an axillary lesion was observed once only, and this did not maturate. If an area of skin has been exposed to undue irritation or pressure immediately preceding the eruptive period, an aggregation of smallpox lesions may occur locally. It is not uncommon to find a ring of lesions on a thigh where it has been constricted by a garter. A cluster of lesions may be found at the back of the neck where a collar stud has compressed the skin over one of the cervical vertebrae. An interesting example of this phenomenon occurred recently in a case under the writer's care. A man with a discrete smallpox eruption exhibited a square area of densely packed vesicles in his interscapular region. Upon investigation his shirt was found to be patched with coarse material, the site of the patch corresponding exactly with the square of lesions. Bed-ridden persons who contract smallpox also tend to have a disproportionately profuse amount of rash across the shoulders and buttocks, but these local peculiarities never modify the essentially centrifugal distribution of the smallpox rash.

The evolution of the eruption. In variola minor the papules are not always palpably deep seated. The hard shottiness so characteristic of classical smallpox is frequently absent, and in these cases reliance may have to be placed on other factors in establishing a diagnosis, e.g. the distribution of the rash. In the vesicular stage of variola minor the lesions sometimes exhibit irregularity in shape; they are not as invariably spherical as in the major variety, but the superficial bleb-like appearance of the chicken-pox lesion is

never seen. The vesicle is firm and unyielding and is definitely *in*, rather than *on*, the skin. The fact that a vesicle is uni- or multi-locular has no diagnostic significance in smallpox, and umbilication of the vesicles has not the slightest value in diagnosis, as it is observed quite as frequently in the lesions of chicken-pox. In smallpox the lesions will be found to be in the same stage of development in any one region. The rash on the face is usually a little in advance of the rash on the limbs, but the co-existence of papules and vesicles, or vesicles and pustules, on the face or limbs never occurs in either form of smallpox, and, if found, definitely excludes this disease. Again, the rash in non-classical smallpox resembles the severer type of the disease in never coming out in crops. In maturation the deep-seated lesions in the palm or sole usually lag behind a little and may take a fortnight to exhibit signs of scabbing, but, as a rule, some scabbing is apparent in the facial lesions within a week of the appearance of the eruption. The rash on the trunk is rarely so well developed as the eruption on the face and limbs. The lesions frequently abort at the vesicular stage, and large scabs are uncommon in this region except when contiguous vesicles have run together, a feature occasionally noticed in this part of the body. Scab formation always begins in the centre of the pustule and spreads outwards. The areola in variola minor is not nearly so neatly defined as in the classical type of smallpox and a blotchiness around the lesions, especially on the trunk, is very often seen.

Course of the disease. In variola minor the appearance of the rash always coincides with an abatement of symptoms. As a rule, the patient feels perfectly well and remains so during the maturation of the rash. Secondary suppurative fever is never observed. In unrecognized cases the patient may continue at his work, and it is this feature of the less severe type which plays so large a part in the dissemination of the disease. In confluent cases there may be serious exudation into the skin of the eyelids, and in these cases the patient may suffer a good deal of local discomfort without corresponding constitutional disturbance. In old age confluent cases may be serious, and fatal results have been recorded, but it is probable that death in these cases was primarily caused by senile degenerative changes, rather than by toxaemia. The mortality from variola minor in this series of cases was nil as compared with thirteen deaths among 222 cases of the classical disease treated at the Cardiff Smallpox Hospital during the years 1903–25. From the aesthetic point of view there is little difference in the appearance of the patient suffering from either variety. In the majority of cases the patient is free of all scabs and fit for discharge from hospital within four weeks from the date of eruption. Confluent or semi-confluent cases require six weeks or longer. Even in the mild discrete cases the 'seeds' in the soles of the feet may persist for many weeks. Rarely bullae occur on the soles, and sometimes the fluid in these is blood-stained. Bullae may attain a large size, but cause little inconvenience if the patient is in bed. As in the classical disease, there is a tendency for boils and mild septic skin conditions to occur in convalescence. No definite sequelae or

complications, other than these minor manifestations, were observed in this series of several hundred cases. Whilst the scars left after variola minor are neither so deep nor so pitted as those resulting from an attack of the classical disease, they are always discernible on careful examination, and this circumstance once enabled the writer to connect up, retrospectively, link by link, the later recognized cases of smallpox with the original unascertained source of infection which had introduced the disease into a district six months earlier.

The infectivity of variola minor. Most observers are agreed that the prevailing type of smallpox has not so high a degree of infectivity as the classical type. In the series here reviewed the contact in all cases had been close, e.g. the secondary cases lived in the same house or had been otherwise closely associated with the source of infection. Casual contact with ambulant cases in the street or at work has failed to infect unprotected individuals in scores of instances within the knowledge of the writer.

The relation of vaccination to variola minor. Recent successful vaccination was found in all cases to afford protection against smallpox. In this series, of those successfully vaccinated in infancy, the youngest case of smallpox was aged 19 years, and no patient had been successfully revaccinated. Vaccination performed within three days of exposure to infection was found to afford absolute protection against variola minor. Vaccination later than this, if successful, was occasionally seen to modify the disease, but this was not invariable. Vaccination performed late in the incubation period most commonly produced no reaction, but occasionally was successful, the two conditions—variola and vaccinia—developing concurrently. Vaccination in the eruptive stage is invariably unsuccessful in both varieties of the disease.

Differential diagnosis. 1. Chicken-pox has always been the disease for which smallpox is often mistaken, and the chances of an error in diagnosis are considerably enhanced by the mild character of the prevailing type of smallpox. A diagnosis should be made independently of constitutional symptoms and personal history, for both are unreliable—especially the latter. No one wants to be labelled as a case of smallpox. Constitutional disturbance in the eruptive period, especially in adults, is much more frequently found in chicken-pox than in variola minor. Most mistakes in diagnosis result from a partial examination of the body. If the practitioner does not make a point of surveying the whole body he cannot assess the relative distribution of the rash with which he is dealing, and relative distribution should be his sheet anchor in the differential diagnosis of rashes resembling smallpox. In the papular stage of variola minor the distribution may be the sole guide in differential diagnosis, as the lesions in the early stages may be indistinguishable from those of chicken-pox. The centrifugal disposition of the smallpox eruption is rarely lacking, and this is just as true of the non-classical as it is of the classical type. This feature alone should enable the practitioner to exclude chicken-pox, but there are other helps. The fact that smallpox lesions on face, arm, leg, or trunk are found all in the same stage of development in each area, whereas in chicken-pox papules,

vesicles and scabs are found side by side in one area of skin, materially assists in the differentiation of the two conditions. The type of lesion and the time interval in maturation are also factors which must be taken into consideration. The superficial bleb-like vesicle of chicken-pox is quite unlike the deeper-seated and firmer looking vesicle of smallpox. Vesicles will be found present on the first day of the eruption in chicken-pox and at least a few scabs the following day, but in smallpox no fully formed vesicles will be found until the third day of eruption and scabs do not appear until the seventh day. Severe cases of chicken-pox with profuse eruptions occasionally cause difficulty in diagnosis, although a consideration of all the factors usually enables a diagnosis to be made with certainty. In such severe cases the lesions may be very thickly disposed on the face, and the limbs (even the hands and feet) may have been invaded. The latter feature is especially seen in hot weather, and in these cases one or two varicellar vesicles on the feet may closely resemble variola. But an examination of the whole body will reveal that the rash in these cases is concentrated upon the trunk and that elsewhere it is less profuse. There is a marked diminution from the trunk to the periphery, and on the limbs the number of lesions lessens from above downwards. The lesions are in all stages. They are superficial in type, stuck on the skin rather than situated in the skin—all features which characterize chicken-pox and which exclude smallpox. In these profuse types of chicken-pox it will often be found that the rash on the trunk has invaded the axilla, where it is extremely rare to find even one smallpox lesion.

2. Syphilitic dermatitis of the papular or papulo-pustular type is occasionally confused with smallpox. In this condition the rash is more profuse on the trunk than on the exposed parts, e.g. face and hands. The syphilitic papules are usually larger and flatter than the variolous. The rash is uniformly distributed over the trunk (front and back) and has, as a rule, a coppery tint; it is usually accompanied by the other characteristic manifestations of syphilis. The blood in this stage will be found to give a strongly positive Wassermann or flocculation reaction, but this evidence is, of course, only corroborative and can never decide the diagnosis. In the pustular syphilides an occasional lesion may mimic variola, but the distribution of the eruption is never centrifugal.

3. Prurigo (summer prurigo, prurigo aestivale) is occasionally mistaken for smallpox, especially during the summer months. The distribution of this condition may closely resemble smallpox, but the lesions are never more profuse on the face than the limbs, and individually they are much smaller and more superficial than those of variola. They are not set in the skin but upon it, and they seldom spontaneously go beyond the vesicular stage, which is usually abortive. Central pinhole scabs occasionally are seen, but by this time the vesicle has largely disappeared. The glands draining the infected area of skin are frequently enlarged in prurigo, especially in the femoral region. Although the previous history of a patient's skin eruptions should not be considered in

excluding variola, the account of similar attacks occurring before serves to confirm a diagnosis of prurigo.

4. Erythema iris is an interesting condition which sometimes raises a suspicion of smallpox in the mind of the medical attendant. The lesions affect the hands, wrists, feet and ankles, but more rarely are also found on the face and even on the mucous membrane of the mouth. The condition develops insidiously, not acutely, and consists of raised papules surrounded by clusters of vesicles. Individual vesicles sometimes simulate the variolous lesion, but the pleomorphism of the lesions readily serves to exclude smallpox. Bullous formation is as frequent in this skin condition as it is rare in smallpox.

5. Erythema multiforme (especially the annular form) sometimes causes trouble in diagnosis, but here again the relative distribution, and the variety of lesion shown, renders a differential diagnosis comparatively simple. The trunk and face are affected more than the limbs in erythema, and, although individual lesions may closely mimic the vesicle of variola, the co-existence of raised red patches of various shapes with vesicles and bullae is sufficient to put smallpox out of court.

6. Acne is occasionally confused with smallpox. It may be of interest to mention that the first case of variola minor to be recognized in the present South Wales epidemic had been treated for a week in the wards of a large general hospital as a case of acne. It is hardly necessary to point out that even severe acne does not affect the periphery of the limbs, and that variolous lesions do not respond to the approved local treatment for acne. It should, however, be borne in mind that the two conditions may co-exist, and acne is a not uncommon complication of the minor variola.

7. Urticarial conditions are sometimes thought to be smallpox. The papular form is the only form of urticaria which in any way resembles variola, but here again relative distribution is usually sufficient to establish the diagnosis. If not, the absence of maturation settles any doubts which may have been entertained. In the writer's experience papular urticaria is very rarely seen on the face.

II. *Epidemiological Considerations.*

Although the clinical manifestations of the non-classical type of smallpox and its relation to vaccination would seem to establish clearly its identity with the classical disease, there can be no doubt that the two types show marked differences in epidemiological behaviour. The contrast in infectivity is striking. In variola minor secondary cases are usually confined to those persons who have been in close contact with the source of infection. That this low degree of infectivity is independent of the vaccinal condition of the community affected appears to be generally accepted. To the mass of evidence available on this point the writer would add his own experience in an industrial town of 50,000 inhabitants almost completely unprotected by recent vaccination. Variola

minor had been existent there unrecognized for three months and had meanwhile spread unchecked. Yet prompt isolation of cases, with supervision of contacts, sufficed to bring the disease under control in two months. The absence of severe constitutional symptoms aids the transmission of the disease by allowing intercourse between infective and susceptible individuals, but these facilities for spreading infection are out of all proportion to the number of cases which subsequently develop smallpox. Thus, a Cardiff child attended school for two days after the rash of minor smallpox appeared. She mixed freely in the playground with hundreds of other children and sat in a classroom with forty classmates, many of whom were unprotected by vaccination, but, although no child was vaccinated after exposure, not a single secondary case occurred. Again, a woman was admitted to the general ward of a Cardiff hospital sickening with variola minor. She developed the rash three days later and lay in that ward with thirty-two other patients for four days more before a suspicion of smallpox was raised, and yet no secondary cases occurred amongst the patients, nursing staff or visitors to that institution—over 1,000 persons. Vaccination in this instance was carried out on the whole hospital population, but it was obviously several days too late to ensure absolute protection. Many other instances might be given to illustrate the relatively low grade of infectivity characteristic of the prevailing type of smallpox. It may be mentioned that approximately 40 per cent. of the school population in Cardiff have never been vaccinated at all, and yet the disease has never taken root in the City, although the infection has been introduced from the surrounding heavily infected areas on over a dozen separate occasions during the last three years.

The all-important question as to whether the non-classical can produce the classical type has been much debated, but on this point a decision has not yet been reached. Whether the present variant will continue to breed true remains to be seen. If, however, it is the case that micro-organisms can alter in virulence by passage through animals, there would appear to be some justification for the belief that the variola virus might under varying circumstances become attenuated or enhanced by passage through human beings. The recognition by bacteriologists that alteration in environment may profoundly modify the cultural and serological characteristics of organisms is a development which may be of great significance in the final elucidation of this problem of variation in virulence.

In the meantime, as it is not certain that the prevailing type of smallpox may not produce the classical, the necessity for control of the disease in communities remains unchanged. To this end prompt segregation of patients and supervision of contacts are the most important means. In view of the longer and more uncertain incubation and pre-eruptive periods, contacts should be kept under observation for at least twenty-one days after their last exposure to infection. Having regard to the negligible mortality of the prevailing type and the disturbing reports concerning post-vaccinal encephalitis, vaccination as an

instrument of prophylaxis should be used with discretion. All the factors should be weighed carefully before a primary vaccination during the period of adolescence is advised. Even when the non-classical type of the disease has assumed epidemic proportions in a community, it is doubtful whether the enforcement of generalized vaccination is ever justifiable.

The history of the disease during the last few years in South Wales is of itself sufficient to warrant the conclusion that the control of variola minor depends, firstly, upon accurate and prompt diagnosis of cases, followed by their speedy removal to a smallpox hospital; and, secondly, upon the careful and complete ascertainment of all contacts, followed by daily supervision of them for a period of not less than three weeks, counting from their last exposure to infection.

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THE SIZE AND SHAPE OF THE HEART IN GOITRE[1]

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With Plates 25 to 29

The Size and Shape of the Heart in Goitre.

In Parry's original description of exophthalmic goitre published in 1825 (50), the importance of the heart lesion was emphasized, and he described what was almost certainly auricular fibrillation, and also enlargement of the heart. Fifteen to twenty years later came the papers of Basedow (4) and Graves (27), which added little, yet both observers found that the heart was sometimes enlarged. To-day cardiovascular changes, though not acknowledged by all (28), are widely admitted to be among the most striking features of thyroid disease; tachycardia is almost invariable, changes in blood-pressure are usual, and auricular fibrillation is common. But the question of enlargement of the heart, its incidence and degree and the particular parts involved, has not often been the subject of special observations.

We have investigated clinically a series of 130 cases of goitre, and have analysed a further series of 43 post-mortem cases from the records of the Pathological Department of the London Hospital, with the limited object of giving some answer to these questions concerning the heart. Under the term goitre we have included all cases in which the secretion of the thyroid gland seemed to be excessive or abnormal, as judged by its effect on the system. The majority of the patients presented the classical symptoms of thyroid intoxication; but there were a few who lacked many of these symptoms, and who would be grouped as cases of 'masked hyperthyroidism', a condition now being more often recognized. The main symptoms of this latter group are cardiac, and the diagnosis is based on the thyroid enlargement, which is often very slight, on the absence of other cause for a heart affection, and (as we shall show) on certain distinctive features of thyro-cardiac disease. Occasionally an estimation of the metabolic rate, or a therapeutic test with iodine, will help to determine the diagnosis. Myxoedema and other hypothyroid states have not been examined.

No attempt at classification into groups such as exophthalmic goitre and toxic adenoma has been made. So many synonymous terms have been applied to thyroid disease, and so many subdivisions have been based on symptoms not fundamental, that a state of chaos equal to that of the classification of renal

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disease has been reached. A reaction against this state of affairs is now setting in, and we believe that this is a move in the right direction (20, 21, 26, 62). Hence we shall refer to all cases simply as *goitre* as defined above. Patients with goitre who also showed signs of other cardiac disease were excluded from the clinical series, but not some with hypertension.

A. *Post-mortem Series.*

This series comprises forty-three goitre cases in which necropsies were performed in the Pathological Department from 1907–29 inclusive. In some of the earlier records, and those made during the war, the details are not so full as in others, for the observations were made in the routine manner and not, of course, with the special objects of this paper in view. The clinical as well as the post-mortem findings on these forty-three cases have been analysed in Table I. There were thirty-five women and eight men; all had enlargement of the thyroid gland, and with three exceptions, to be described later, all had presented during life the classical picture of thyroid intoxication. Wasting, nervousness, and tachycardia occurred in all, tremor in all but one, and exophthalmos in all but five. Malignant thyroid disease is not included. Only two examples of tracheal stenosis were recognized. The high proportion of operation deaths in this series will be readily understood when the early period from which the records date is taken into consideration.

Hypertrophy of the heart, in part or in whole, was specified in twenty-two out of the forty-three cases, i.e. about half; and the heart-weight was considerably above normal in two others (Cases 29 and 39). The heart was described as follows:—

General hypertrophy	12
Left ventricle only	5
Both ventricles, left especially	3
*Right heart and left auricle	1
Left ventricle and left auricle	1

* Complicated by slight chronic mitral endocarditis and stenosis.

The average body-weight in these twenty-two cases (omitting two in which the measurement was not made) was 86 lb. (39 kg.), and the average heart-weight 11·3 oz. (321 grm.). The average age was 37, and average duration of symptoms was 1·9 years.

In the remaining twenty-one cases, in which there was no definite statement as to the presence of hypertrophy, the average age was 29, and the average duration of symptoms 1·3 years. The average body-weight was 88 lb. (40 kg.), and that of the heart 9·66 oz. (274 grm.); in these are included four hearts described as showing brown atrophy, and one in which the left ventricle was dilated. The heart-weight was recorded after washing the specimen, the large vessels being cut across close to the heart. The coronary arteries were always free of anything but the slightest atheroma, with one exception (Case 38). Rheumatic heart disease was only certainly found once (Case 20), where there was fibrosis and stenosis of the mitral valve.

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TABLE I

Summary of Clinical and Post-mortem Findings in Forty-three Cases of Goitre.

Abbreviations: N. R. = normal rhythm.
A. F. = auricular fibrillation.
P. A. F. = paroxysmal auricular fibrillation.
L. V. = left ventricle.
R. V. = right ventricle.
L. A. = left auricle.
R. A. = right auricle.
* From records other than those of the London Hospital.

Case No.	Age.	Sex.	Goitre Present.	Symptoms.	Rhythm.	Cause of Death.	Body-weight.	Heart-weight.	Abnormalities of Heart.
1	30	F	1 year	1 year	N. R., A. F. 1 day before death	Haemolytic anaemia; Graves' disease	130 lb. 59 kg.	11¼ oz. 319 grm.	Fatty 'tigering' and icterus of myocardium
2	18	F	'Years'	1 year	N. R.	Died day after partial thyroidectomy; Graves' disease	53 lb. 24 kg.	8 oz. 227 grm.	Milk spot on R.V.
3	42	F	18 months	3 years	N. R.	Intestinal haemorrhage; purpura; Graves' disease	122 lb. 55·4 kg.	13¾ oz. 390 grm.	L. V. hypertrophied; milk spots on R. and L. V., slight fatty 'tigering' of myocardium
4	19	M	3 months	3 months	N. R.	Death on day of thyroidectomy; Graves' disease	104 lb. 47 kg.	10½ oz. 298 grm.	—
5	30	M	1 year	1 year	N. R.	Graves' disease	102 lb. 46 kg.	10¾ oz. 305 grm.	Milk spot on R. V.
6	19	F	6 years	5 years	N. R.	Died day after partial thyroidectomy; Graves' disease	106 lb. 48·2 kg.	12½ oz. 355 grm.	Moderate hypertrophy of L. V.; less of other chambers; focal areas of fibrosis in papillary muscle of mitralis; large and small milk spots, and fibrous tags on R. V.

TABLE I (*continued*).

Case No.	Age.	Sex.	Goitre Present.	Symptoms.	Rhythm.	Cause of Death.	Body-weight.	Heart-weight.	Abnormalities of Heart.
7	20	F	1 year	9 months	N. R.	Acute pancreatitis; died day after partial thyroidectomy; Graves' disease	105 lb. 47·7 kg.	10 oz. 284 grm.	—
8	19	F	?	18 months	N. R.	Died day after laparotomy; no cause discovered for abdominal symptoms; Graves' disease	127 lb. 58 kg.	10 oz. 284 grm.	—
9	27	F	?	3 years	N. R. (congestive failure)	Broncho-pneumonia; Graves' disease	108 lb. 49 kg.	10¾ oz. 305 grm.	—
10	31	F	10 years	1 year	N. R.	Graves' disease	67 lb. 30 kg.	8¾ oz. 248 grm.	Slight relative hypertrophy of L. V.; milk spots on R. V.
11	22	F	?	7 months	N. R.	Broncho-pneumonia; Graves' disease	90 lb. 41 kg.	9½ oz. 270 grm.	—
12	26	F	?	'Years'	N. R., A. F. on day before death	Broncho-pneumonia; Graves' disease; widely disseminated miliary tuberculosis; calcareous mesenteric glands	83 lb. 38 kg.	8½ oz. 241 grm.	—
13	14	F	?	Few weeks	N. R.	Lobar pneumonia; Graves' disease; old operation; partial thyroidectomy	62 lb. 28·2 kg.	8 oz. 227 grm.	Moderate hypertrophy of heart, particularly L. V.; large milk spot on R. V.
14	42	F	1 month	1 month (cough 6 months)	A. F. (congestive failure)	Acute and chronic heart failure; Graves' disease	104 lb. 47 kg.	13 oz. 369 grm.	Great dilatation of R. V. and R. A.; considerable dilatation of L. V.
15	46	F	10 years	10 years	N. R.	Acute gastro-enteritis; Graves' disease	81 lb. 36·8 kg.	11¼ oz. 319 grm.	Hypertrophy of all chambers, especially L. V.; both auricles dilated; milk spots on R. V.

16	50	M	?	4 years	A. F.	Broncho-pneumonia; Graves' disease	160 lb. 22·7 kg.	16 oz. 454 grm.	Marked hypertrophy and considerable dilatation of all chambers; a few milk spots and fibrous tags on pericardium
17	22	F	?	2 years	N. R.	Broncho-pneumonia; Graves' disease	56 lb. 25·4 kg.	8 oz. 227 grm.	—
18	28	F	6 months	5 months	N. R. A. F. after operation; died next day	Broncho-pneumonia; partial thyroidectomy	67 lb. 30 kg.	7¾ oz. 220 grm.	Milk spot on L V.
19	57	F	3 years	2 years	A. F.	Broncho-pneumonia; marasmus; Graves' disease	61 lb. 27·7 kg.	9 oz. 256 grm.	Slight hypertrophy of all chambers relative to body-weight; milk spots on R. V.
20	48	F	?	?	A. F.	Broncho-pneumonia; chronic rheumatic endocarditis; Graves' disease	97 lb. 44 kg.	10½ oz. 298 grm.	Slight hypertrophy and dilatation of L. A., R. V., and R. A.; chronic rheumatic endocarditis and slight stenosis of mitral valve; large milk spot on R. V.
21	35	F	12 years	5 years	Parox. A. F.	Broncho-pneumonia; lateral compression of trachea; multiple adenomata of thyroid	73 lb. 33·1 kg.	8¼ oz. 234 grm.	Brown atrophy; large milk patch on R. V.; fibrous granules on R. A.
22	23	F	3 years	6 months	N. R.	Broncho-pneumonia; died 2 days after partial thyroidectomy; Graves' disease	85 lb. 38·5 kg.	9½ oz. 270 grm	Hypertrophy of L. V.; (L. V. 1·4 cm.; R. V. 0·3 cm. thick)
23	22	F	2 years	2 years	N. R.	Broncho-pneumonia; died 3 days after partial thyroidectomy	82 lb. 37·2 kg.	9½ oz. 270 grm.	Slight hypertrophy of L. V.; (L. V. 1·3 cm.; R. V. 0·3 cm. thick)
24	26	F	11 months	7 months	N. R. (congestive failure)	Marasmus; Graves' disease	58 lb. 26·3 kg.	7¼ oz. 206 grm.	Atrophied

TABLE I (*continued*).

Case No.	Age.	Sex.	Goitre Present.	Symptoms.	Rhythm.	Cause of Death.	Body-weight.	Heart-weight.	Abnormalities of Heart.
25	29	F	1 month	1 month	N. R.	Broncho-pneumonia; acute pericarditis; septicaemia; chronic empyema; Graves' disease	67 lb. 30 kg.	12¼ oz. 348 grm.	Slight hypertrophy and dilatation of L. V., R. V., and R. A.; very slight deposit of fibrin on pericardium
26	55	M	15 years	5 months	A. F.	Purulent bronchitis; lateral compression of trachea; died 1 day after partial thyroidectomy; colloidal and parenchymatous goitre	90 lb. 39·5 kg.	9¼ oz. 263 grm.	Brown atrophy; milk spot on pericardium
27	20	F	1 year	1 year	N. R.	Goitre; died during thyroidectomy	124 lb. 56·3 kg.	12 oz. 341 grm.	*Hypertrophy of L. V.
28	60	M	?	2 years, 2 months	A. F. (congestive failure)	Goitre	122 lb. 55·4 kg.	14¾ oz. 418 grm.	*Considerable hypertrophy of L. V.; slight of R. V.
29	33	M	17 years	3 years	N. R.	Died 3 days after partial thyroidectomy; multiple adenomata of thyroid	113 lb. 51·3 kg.	13½ oz. 383 grm.	—
30	35	F	?	2 years	N. R.	Graves' disease	73 lb. 33·1 kg.	7 oz. 199 grm.	Slight hypertrophy of L. V. (wall = 2 cm. thick) and L. A.
31	34	F	?	1 year	N. R.	Fibrino-purulent pericarditis; myasthenia gravis; goitre	81 lb. 36·7 kg.	10¾ oz. 305 grm.	7 c.c. pus in pericardial sac; thin layer of fibrin on pericardium
32	20	F	?	7 months	N. R., A. F. after thyroidectomy	Broncho-pneumonia; Graves' disease; died 11 days after partial thyroidectomy	?	8¼ oz. 234 grm.	—

33	27	F	1 year	1 year	N. R.	Died day after partial thyroidectomy; Graves' disease	?	10½ oz. 298 grm.	Slight hypertrophy of all chambers; milk spots on pericardium
34	24	F	11 months	1 year	N. R.	Marasmus; Graves' disease	53 lb. 24 kg.	9 oz. 256 grm.	—
35	41	F	2 years	11 months	A. F. (probably congestive failure)	Graves' disease	?	13 oz. 369 grm.	Hypertrophy and dilatation of L. V. and L. A.
36	30	F	3 months	3 months	N. R. (congestive failure)	Terminal acute infective endocarditis; Graves' disease	105 lb. 47·7 kg.	13½ oz. 383 grm.	Considerable hypertrophy of both ventricles; minute vegetations on mitral valve; engorged, inflamed spleen (20 oz.)
37	40	F	?	8 months	N. R.	Graves' disease	88 lb. 38·5 kg.	9 oz. 256 grm.	Slight dilatation of L. V.; subendocardial haemorrhages in L. V.
38	63	F	?	None	A. F.	Heart failure; fibrosis of myocardium; Graves' disease; muco-purulent cholangitis; chronic cholecystitis and cholelithiasis	96 lb. 43·6 kg.	11¼ oz. 319 grm.	Fine fibrous adhesions between two layers of pericardium; R. A. hypertrophied and dilated; L. A. dilated; moderate dilatation and hypertrophy of R. V.; patchy microscopic fibrosis of myocardium, probably scarred rheumatic myocarditis
39	25	F	12 years	None	N. R.	Died immediately after almost complete thyroidectomy; marked lateral compression of trachea; colloidal goitre	98 lb. 44·5 kg.	13¾ oz. 390 grm.	—
40	63	M	12 years	None	A. F.	Bilateral pyonephrosis; urethral stricture; colloidal adenoma (7 × 5 × 3 cm.) above and not attached to the upper pole of the right lobe of a normal thyroid	104 lb. 47 kg.	10¾ oz. 305 grm.	Brown atrophy

TABLE I (*continued*).

Case No.	Age.	Sex.	Goitre Present.	Symptoms.	Rhythm.	Cause of Death.	Body-weight.	Heart-weight.	Abnormalities of Heart.
41	33	M	2 years	2 years	N. R.	Goitre	62 lb. 28·2 kg.	8½ oz.	*Thickness of V. walls probably unaltered; slightly thick for body-weight; milk spot 3·5 × 2 cm. on R. V.
42	48	M	5 years	5 years	N. R.	Partial thyroidectomy; Graves' disease	93 lb. 42·2 kg.	12½ oz.	Milk spot on R. V., 3·5 × 2·5 cm., one on L. V. 1·5 cm. diameter; slight general hypertrophy of heart. L. V. = 1·5 cm. R. V. = 0·5 cm.
43	33	F	'Always had a full throat'	1 year	N. R.	Goitre	52 lb. 23·6 kg.	8 oz.	*Heart not atrophied, but appears large for the condition of the patient. L. V. = 1·1 cm. R. V. = 0·35 cm.

Congestive failure. There were signs of congestive heart failure during life in six cases, three with normal rhythm (Cases 9, 24, and 36 in Table I), and three with auricular fibrillation (Cases 14, 28, and 35). Failure was diagnosed from oedema and enlargement of the liver in all but one, in which it was based on liver enlargement only.

In cases with failure and normal rhythm, the average heart-weight was 10·3 oz. (293 grm.), and the average body-weight 90 lb. (41 kg.). In two of the three with auricular fibrillation the corresponding measurements were 13·6 oz. (386 grm.) and 113 lb. (51 kg.).

Rhythm. The rhythm remained normal till death in thirty out of the forty-three cases. In an additional five it was normal until a few hours or days before death, auricular fibrillation occurring as a terminal event. In this group with normal rhythm, or normal rhythm and terminal fibrillation, the average age at death was 27 years. The average body-weight was 84 lb. (38 kg.), and that of the heart 9·8 oz. (278 grm.). In fifteen of these thirty-five cases the heart was described by the pathologist as hypertrophied.

In eight cases there was established auricular fibrillation of at least a few weeks' duration, though the total duration was uncertain. The diagnosis of this arrhythmia was made on clinical grounds alone in six and by an electrocardiogram in two cases. A rapid, very irregular heart, especially if associated with congestive failure, has been taken as reasonable evidence of fibrillation. The average age at death was 50; the body-weight 104 lb. (47 kg.), and the heart-weight 11 oz. (313 grm.). In six cases the heart was hypertrophied, and in the remaining two it was not so described.

TABLE II.

Post-mortem cases Classified according to Rhythm.

Normal Rhythm: 35 cases (5 with terminal auricular fibrillation).

Average age at death	= 27
„ body-weight	= 84 lb. (38·8 kg.)
„ heart-weight	= 9·8 oz. 278 grm.
Number of hearts described as hypertrophied	= 15

Established Auricular Fibrillation: 8 cases.

Average age at death	= 51
„ body-weight	= 104 lb. (47 kg.)
„ heart-weight	= 11 oz. (313 grm.)
Number of hearts described as hypertrophied	= 6

The frequency of fibrillation in goitre is probably much higher than the number in this series indicates; for it has recently become apparent that fibrillation may often be the result of the toxic action of a very small or imperceptible goitre and in a patient who shows none of those striking ocular or nervous changes which almost alone have served to direct attention to the thyroid in the past.

Cases 38, 39, and 40 differ from the others in the series in that they were not recognized in life as examples of heart disease due to goitre.

Case 38, a woman aged 63, had had dyspnoea for two years before admission, and had been told that she had heart disease. She gave a history of two attacks of jaundice, one ten months and one two weeks before admission. She was found to have auricular fibrillation, an enlarged liver, and gall-stones (X-ray). Quinidine restored normal rhythm, but the patient suddenly died. At post-mortem a large fleshy thyroid containing a little colloid was found, and the heart showed general hypertrophy.

Case 39, a girl of 25, had a goitre removed when she was 13. When she was 16 it started to grow again and gradually increased for a year, when it was the size of a large coconut. At the age of 25 she was admitted for thyroidectomy; there was no wasting, no exophthalmos; the pulse was regular, rate 100. Death from shock occurred after the operation. At necropsy a large heart weighing 13¾ oz. (body-weight 98 lb.) was found.

Case 40, a man of 63, admitted for urinary symptoms, had a 12-years-old goitre which, he said, had given him no trouble. He had an irregular pulse, with a rate of 88–138 (probably A. F.). He died suddenly the day after admission. At necropsy the heart weighed 10¾ oz. (body-weight 104 lb.).

Comment. In this series of forty-three cases there were twenty-two described as having hypertrophy of the heart and twenty-one which were not so described. But it is possible that hearts in the latter group should be considered as relatively enlarged when the age, sex, and body-weight are taken into account. The average age was 29, and there was a definite predominance of women, namely, sixteen to only five men. The average body-weight was 88 lb. (40 kg.), and the heart-weight 9·66 oz. (274 grm.). Walmsley (61) gives the average heart-weight in the male as 11–12 oz. (312–341 grm.) and 10–12 oz. (284–341 grm.) in the female. Between the ages of 15 and 20, however, according to German authors (quoted by Walmsley), the usual weights are 215–236 grm. (Müller) and 200–298 grm. (Vierordt). In accordance with these figures the heart-weights are about normal in the twenty-one cases under consideration. But as there is a large majority of young adult females, the group may include some with relative hypertrophy, e.g. in Cases 29 and 39. On the other hand there are some instances where the heart is definitely not hypertrophied, or is even atrophied (Cases 18, 24, and 26).

The finding of large milk patches or definite pericardial thickening over the right ventricle in six of the cases is not without interest. A loud systolic murmur, often rough in character, over the pulmonary area, and that part of the chest-wall overlying the right ventricle, is frequent in goitre. It is said to be sometimes to and fro, which would be in favour of a pericardial origin.

B. *Clinical Series.*

The clinical series was unselected in that every patient with goitre producing symptoms, who was seen in hospital or private practice during the period of study, was included. It is admitted that there were a number of severe cases, such as would be referred to a cardiographic department or considered for surgical treatment, but patients of every grade of severity were investigated. Table IV indicates the scope of the clinical inquiry.

The size of the heart may be estimated by clinical methods or by means of X-rays. The clinical method is especially fallacious in goitre cases, as the rapid and forcible heart action produces a widely diffused impulse, which easily creates a false impression of enlargement. Only when the apex-beat is felt as a definite lift outside the nipple line is it possible to be certain of enlargement, and not even then if the rate is excessive. We have relied on radiological methods, therefore, in determining the size of the heart.

In orthodiagraphy, the heart and chest outlines are projected on to the fluorescent screen by moving around them a narrow pencil of rays the axis of which is always perpendicular to the screen, and the heart outline is drawn by the observer. In this way a true-sized outline of the heart is obtained. The method has the drawback of introducing a personal factor, and thus involving a slight degree of error, but it has the advantage of permitting inspection of the heart's pulsation while the record is being made, and of being easily and quickly combined with ordinary screen examination in the various oblique positions. Observation of pulsation is important as its timing gives a clue to the part of the heart involved, and differences in pulsation greatly facilitate the accurate delimitation of individual arcs and their measurement.

In teleradiography a photographic record is taken with the film at a distance of six feet from the tube, when the rays are almost parallel. This method partly eliminates the personal factor, though it still enters into the centring of the tube and of the patient. The picture of the heart obtained is almost true-sized, and as the degree of distortion in six-foot films is approximately constant it may be ignored in comparing one with another. Shadows and outline often show more detail in films than on the screen, and so can be more easily interpreted. Each method has its own special advantages and limitations, and we have accordingly combined the two. All cases were screened, and in nearly all orthodiagrams and teleradiograms were taken. The diagnosis of enlargement was never based on screen examination alone.

Criteria of enlargement. Simple inspection of the X-ray picture, taken by either of the methods we have used, will often show at once whether the heart is enlarged or not. Anyone constantly engaged in examining X-ray pictures, normal and pathological, cannot fail to acquire a facility for detecting departures from the normal.

In some cases, however, the presence or absence of enlargement will be a matter of divergent opinion if inspection only is used, and here measurements must be made and compared with the published table of normals. In these tables, heart-size is correlated with body-weight, as the ratio of heart-weight to body-weight has been shown by anatomical observations to be fairly constant. From the frontal silhouette the total transverse diameter, and the oblique (or long) diameter can be obtained, and of these two the first is both more often measurable and more useful as an indication of heart size. In the normal chest the total transverse diameter of the heart bears a fairly close relation to the maximum (internal) transverse diameter of the chest, or, in other words, to the

greatest horizontal diameter of the lungs. This ratio, $\frac{\text{internal chest diameter}}{\text{horizontal heart diameter}}$, is given by Hammer (31) as 1·7 to 2·2 in adult men, and 1·92 to 2·15 in adult women. Danzer (17) gives a ratio of 1·9 to 2·6 based upon 500 normals. Variations in the heart lung ratio depend mainly on the shape of the chest and the lie of the heart. In a short wide chest with a horizontal type of heart the ratio will be at the lower normal limit, the transverse diameter of the heart being relatively large. In a long narrow chest with a vertical type of heart the ratio will be at the upper limit of normal, the transverse diameter of the heart being relatively small. Thus in the case of the vertical heart considerable enlargement may occur before the heart-lung ratio falls below the normal limit. The lung diameter is measured at the widest part from the line of junction of the chest-wall and lung translucence above the highest part of the diaphragm. Usually, but not always, the greatest lung diameter is at the base of the chest just above the diaphragm; sometimes the chest is constricted at this point, the widest part being situated at a slightly higher level.

Three tests were used in deciding whether a heart was pathologically enlarged or not: simple inspection of the orthodiagrams, determination of the cardio-thoracic ratio, and comparison of the total transverse diameter of the heart actually measured with that predicted as normal for the body-weight by published tables.

1. *Inspection of the orthodiagram.* Unless enlargement was suspected by the first test, i.e. on inspection, further tests were not applied.

2. *Cardio-thoracic ratio.* When the cardio-thoracic ratio for all such cases (i.e. with apparent enlargement) was calculated, it always proved to be less than 2. But this ratio varies in normal individuals with the lie of the heart and the shape of the chest, so that a ratio of less than 2 is acceptable evidence of enlargement only when the chest is of average or narrow width. In a short wide chest a ratio below 2 need not mean enlargement. Yet, of the seventeen cases with apparent enlargement where the chest was wider than the average, the cardio-thoracic ratio only once exceeded 1·7, so that these too may be reckoned as enlarged. The effect of bodily wasting on the cardio-thoracic ratio must be mentioned. By lowering the diaphragm the heart becomes more vertical and the transverse diameter diminishes, while the chest diameter remains unaffected. Thus a heart of given size will tend to have a higher cardio-thoracic ratio in a wasted subject than in one normally nourished. The estimation of enlargement by means of the cardio-thoracic ratio in a series of wasted subjects will therefore be a conservative one.

3. *Transverse heart diameter.* The observed transverse heart diameter is compared with those given in published tables. There are available several well-known tables of average measurements in normal men and women, giving a maximum, average, and minimum for groups of particular weight, height, age, and sex. It is now generally agreed that body-weight is the best guide. In ordinary cardiological practice these figures have not been found as useful as

had been hoped, largely because the maximum and minimum in the tables are often so wide apart. An orthodiagram showing obvious enlargement on inspection, and with full clinical support for this view, may yet be below the maximum for the appropriate weight category given in a table. Moreover, authorities give different figures; to illustrate with an extreme instance, the observed heart diameter in one particular case was more than the maximum given in one table, but below the minimum in another.

An attempt was made to compare the transverse measurements in our series with those given by (1) Hammer (32), (2) Vaquez and Bordet (60), and (3) Schinz and others citing Dietlen, (53). Notwithstanding the above criticisms it was found that of our cases in which a comparison was possible, the maximum normal was exceeded in 23 per cent. (ten cases) in Hammer's table, 62 per cent. (twenty-one cases) in Vaquez and Bordet's table, and 40 per cent. (twenty cases) in Schinz and others' table. Further results are given below.

Table showing how the transverse diameters in our series of enlargement compare with the normal figures given by Hammer, Vaquez and Bordet, and Schinz (subject standing).

		No. of Cases.
Hammer	Over maximum	10
	Equal to maximum	2
	Over average	10
	Equal to average	1
	Over minimum	19
	Less than minimum	1
	Total	43
Vaquez and Bordet	Over maximum	21
	Over average	11
	Over minimum	2
	Total	34
Schinz and others	Over maximum	20
	Equal to maximum	6
	Over average	9
	Equal to average	3
	Over minimum	6
	Less than minimum	5
	Total	49

A question arises as to the validity of applying a standard of heart-size based chiefly on body-weight, to cases presenting great wasting. This would have the effect of producing apparent or relative enlargement; since, however, loss of weight will tend to reduce the transverse heart diameter as explained above (lowering of the diaphragm), the two influences are opposed and will more or less balance each other.

Table III gives the incidence of enlargement in the total 130 cases as judged by inspection of the orthodiagram and by the estimation of the cardio-thoracic index. The measurements were made in nearly all cases on orthodiagrams taking in the standing posture, as nearly as possible in the

mid-respiratory position (i.e. with the diaphragm in the mid-position between expiration and inspiration, the patient breathing as quietly as possible). The table shows that enlargement was present in about 45 per cent. of cases, the average age of those with enlargement being definitely, though slightly, greater than of those without. The average duration of symptoms is seen to be nearly twice as long in those with enlargement. Goitre was present before the development of symptoms in a larger percentage of those with enlargement than in those without. The incidence of complete arrhythmia is very different in the two groups. The heart was never normal in size when auricular fibrillation had been established for more than a few weeks; but paroxysmal fibrillation did occur in five cases with hearts of normal size. Fibrillation (established in the great majority) was present in about half of the enlargement group; and in this group was one with auricular flutter.

TABLE III.

Showing Relation between Enlargement, and the Age, Duration of Symptoms, and Rhythm (Clinical Series).

(1) *No enlargement (or doubtful)*	71 (54·6 %)
Average age	39 years
Average duration of symptoms	1·7 years
Rhythm:—	
Normal	66
Paroxysmal A. F.	5
Established A. F.	0
(2) *Enlargement*	59 (45·4 %)
Average age	47 years
Average duration of symptoms	3·25 years
Rhythm:—	
Normal	29
A. F. (paroxysmal or established)	29
Auricular flutter	1

The degree of enlargement was as a rule moderate. Considerable increase in size was seen only in those cases with fibrillation and congestive failure, and in a few with associated high blood-pressure. Both left and right sides of the heart contour may be extended, and nearly always the increase in size was bilateral. In some the enlargement appeared entirely to the left, when it was usually associated with changes in the pulmonary arc to be described later; but the boot-shaped contour characteristic of aortic incompetence or hypertension was never seen.

Progressive change in the size of the heart. We have been able to get serial records in a few cases which demonstrate the development of enlargement over a period of six months to three years. In all of these permanent fibrillation was present; and augmentation of the transverse diameter varied from 1·5 cm. to over 4 cm., both contours of the heart being equally affected by the change.

TABLE IV

Analysis of Clinical Series

Abbreviations.

L. = left.
R. = right.
L. P. = laevogram predominates.
D. P. = dextrogram predominates.
No predom. = no predominance.
V. P. Cs. = ventricular premature contractions.
Aur. P. Cs. = auricular premature contractions.

The figures in the right-hand column refer to heart-rate.

Case No.	Age.	Sex.	Cardiac Enlargement.	Pulmonary Arc.	Duration of Symptoms.	Blood-Pressure.	Electrocardiogram.
1	30	F	+(L.)	Sl.+	3 years	160/50	N.R., 140, no predom., P > T
2	23	F	?	?+	4 years	145/60	—
3	25	M	None	Not+	1 year	140/90	—
4	23	F	+(L. & R.)	Not+	4 years	140/60	N.R., 160, L.P., P = T
5	45	M	None	Not+	2 years	120/50	N.R., 125, D.P., P+
6	38	F	?	Sl.+	Few weeks	—	A.F., 95, D.P.
7	18	F	None	Sl.+	3 months (goitre one year)	130/0	—
8	20	F	?	+	19 months	155/30	N.R., no predom., P+
9	42	F	+(L. & R.)	Not+	5 months	150/90	—
10	56	M	+(L. & R.)	?	8 months	180/70 (with N.R.)	A.F., 120, L.P.
11	30	F	None	?	1 year	135/100	N.R., 95, D.P., T = P
12	38	F	+(L. & R.)	++	2 years	—	A.F., 200, no predom.
13	53	F	+(L.)	+	27 years	145/85	N.R., 110, no predom., T > P
14	32	F	None	?	6 years	150/95	—
15	36	F	None	Sl.+	15 months	—	N.R., 100, no predom., T > P
16	50	F	None	Not+	?	130/90	N.R., normal
17	49	M	+(L.)	Sl.+	4½ years	140/60	N.R., no predom.
18	46	F	+(L. & R.)	Not+	18 months	—	A.F., 100, L.P.
19	56	M	None	Not+	6 months	150/80 (with N.R.)	A.F., 120, ectopic ventricular beats; D.P.
20	49	F	+(L. & R.)	+	18 months	—	A.F., 140, D.P.
21	36	F	None	Not+	6 months	165/85	N.R., 125, L.P.
22	40	F	+(L. & R.)	Not+	2 years	160/80	N.R., 130, no predom.
23	58	F	?	Not+	1 year	140/90	N.R., 90, bundle-branch block
24	42	F	?	Not+	?	—	N.R., 100, no predom.

TABLE IV (*continued*).

Case No.	Age.	Sex.	Cardiac Enlargement.	Pulmonary Arc.	Duration of Symptoms.	Blood-Pressure.	Electrocardiogram.
25	33	M	None	+	2 years	—	N. R., 130, no predom., P > T
26	55	F	+ (L.)	+	18 months	—	A. F., 110, D. P.
27	55	F	+ (L. & R.)	+	5 years	—	A. F., 110, no predom.
28	49	F	+ (L. & R.)	+	11 years	130/90	N. R., 100, L. P., T > P
29	41	F	?	+	1 year	135/75	N. R., 125, D. P., P+
30	52	F	+ (L. & R.)	+	8 years (goitre 13 years)	—	A. F., 100, no predom.
31	33	M	+ (L. & R.)	Not+	21 months	120/65	N. R., 140, D. P., P = T
32	50	M	+ (L. & R.)	+	21 months	—	A. F., 160, L. P.
33	52	F	+ (L. & R.)	Not+	5 months	—	N. R., normal
34	61	F	?	Not+	Few months	90/60	N. R., 125, no predom., T = P
35	40	F	+ (L. & R.)	Not+	4 years (goitre 10 years)	—	N. R., 110, no predom.
36	34	F	+ (L.)	+	?	—	N. R., 90, no predom.
37	54	F	None	Not+	3 years	180/120	N. R., 150, L. P.
38	27	F	None	?	2 years	125/65	N. R., 160, no predom., P+
39	68	F	+ (L. & R.)	?	3 years	—	A. F., 130, D. P.
40	41	F	+ (L.)	+	2 years	130/80	N. R., 140, no predom., ectopic ventricular beats, T > P
41	44	F	None	Not+	Few months	—	N. R., 130, no predom.
42	41	F	?	Not+	9 months (goitre 12 years)	150/90	N. R., 110, no predom.
43	31	F	+ (L. & R.)	+	2 years	150/85	N. R., 150, no predom., P+
44	53	F	?	Not+	3 years (goitre 18 years)	170/100	N. R., 100, no predom.
45	60	M	?	Not+	18 months	160/85	N. R., 120, L. P., P–R just exceeds 0·2 sec.
46	58	M	+ (L.)	Not+	1 month (onset A. F.) ? goitre 15 years	—	A. F., 120, L. P.
47	35	F	None	+	4 months (relapse)	160/100	N. R., 130, no predom., T_2 flat, T_3 neg.
48	56	M	+ (L. & R.)	?	2 years	—	A. F., V. P. C., L. P.
49	41	F	? (L.)	Not+	5 years (goitre 9 years)	175/95	N. R., 120, no predom.

TABLE IV (*continued*).

Case No.	Age.	Sex.	Cardiac Enlargement.	Pulmonary Arc.	Duration of Symptoms.	Blood-Pressure.	Electrocardiogram.
50	56	F	?	Not +	Thyroid + over 30 years; 6 years ago symptoms of hyperthyroidism; present attack 3 months	165/95	N. R., 90, normal
51	20	F	?	Not +	4 years	155/70	N. R., 150, L. P., T > P
52	40	F	None	Not +	2½ years	160/85	N. R., 110, no predom., T > P
53	71	F	+ (L.)	Not +	2–3 years	—	A. F., 150, L. P.
54	61	F	+ (L.)	Not +	18 months	—	A. F., L. P., many V. P. Cs.
55	36	F	None	Not +	12 years	130/85	N. R., S. T., no predom., P +
56	61	F	+ (L.)	? +	6 months	160/80	A. F., D. P.
57	33	F	+ (L. & R.)	Not +	10 months (goitre 11 years)	—	A. F., 120, no predom., V. P. Cs.
58	45	F	+ (L. & R.)	+	3 years	205/85	N. R., 90, no predom.
59	60	F	+ (L. & R.)	+	16 months	170/80	N. R., 100, no predom., T = P
60	59	F	+ (L. & R.)	Not +	2 years (goitre since age 20)	—	A. F., 150, no predom.
61	37	F	None	Not +	18 months (goitre several years)	135/80	N. R., 100, no predom.
62	53	F	+ (L.)	? +	2 years (goitre 20 years)	—	A. F., 130, no predom.
63	69	F	+ (L.)	Not +	2 years (? goitre since a child)	225/110	N. R., 100, L. P., V. P. Cs.
64	55	F	+ (L.)	Not +	2 years (goitre 20 years)	200/130	A. F., 160, L. P.
65	35	F	None	Not +	2 months (goitre 2–3 years)	150/80	N. R., 140, no predom., P > T
66	34	F	+ (L. & R.)	? +	18 months	185/100	N. R., 160, L. P., V. P. Cs.
67	68	F	?	Not +	On and off 6 years (goitre since age 15)	200/90	N. R., L. P.
68	17	M	None	Not +	Few days	150/90	N. R., 130, no predom.
69	53	F	+ (L. & R.)	Not +	6 years (goitre 18 years)	175/110	N. R., 75, L. P., P +
70	52	F	+ (L. & R.)	?	2 years	150/?	N. R., 90, no predom.

TABLE IV (*continued*).

Case No.	Age.	Sex.	Cardiac Enlargement.	Pulmonary Arc.	Duration of Symptoms.	Blood-Pressure.	Electrocardiogram.
71	53	F	+(L. & R.)	Not+	2 years (goitre 6 years)	—	A. F., 115, no predom.
72	45	M	?	Not+	Few days (goitre 3 years)	185/105	N. R., 95, L. P., P+
73	38	F	?	?	5 years	150/90	N. R., 90, no predom.
74	27	F	None	Not+	18 months	125/85	N. R., 90, L. P.
75	50	F	+(L. & R.)	?	7 years	160/80	N. R., 130, L. P., P+ (also P. A. F.)
76	53	F	+(L.)	?	'Many years'	—	N. R., 140, no predom.
77	50	F	?	?	15 years	180/120	N. R., 80, L. P.
78	16	F	+(L. & R.)	+	9 months	150/90	N. R., 125, no predom., P+
79	49	F	+(L.)	+	2½ years	130/85	N. R., 140, L. P., P+
80	42	F	+(L. & R.)	+	1 month	140/70	N. R., 125, L. P., P+ (also P. A. F.)
81	60	F	+(L.)	+	5 months	190/115	N. R., 95, no predom., auricular P. Cs.
82	59	F	?	Not+	6 years (goitre since childhood)	220/110	N. R., 110, no predom., P+
83	48	F	+(L. & R.)	+	2 years (goitre 23 years)	140/85	N. R., 80, L. P.
84	37	F	None	?	1 year	130/90	N. R., L. P.
85	36	M	?	?	3 years	—	A. F., 130, D. P.
86	57	M	+(L. & R.)	Not+	2 years	—	A. F., 70, no predom.
87	51	F	?	Not+	18 months	140/80	N. R., 75, no predom.
88	55	F	+(L.)	+	6 weeks (goitre 5 years)	—	A. F., 140, D. P.
89	56	M	?	+	9 months (goitre 7 years)	180/70	N. R., 130, D. P.
90	60	F	None	?	2 years	—	A. F., no predom.
91	24	M	None	Not+	6 months	140/60	N. R., 120, no predom.
92	20	F	None	?	18 months	140/95	N. R., 150, no predom., P+
93	10	F	None	Not+	3½ years	—	N. R., 75, no predom.
94	43	F	+(L.)	+	20 years	—	N. R., 120, no predom. (also P. A. F.)
95	43	F	None	?	3 months	140/80	N. R., 160, no predom.
96	27	F	None	+	2 months	120/80	N. R., 145, no predom., P+

TABLE IV (*continued*).

Case No.	Age.	Sex.	Cardiac Enlargement.	Pulmonary Arc.	Duration of Symptoms.	Blood-Pressure.	Electrocardiogram.
97	18	F	None	+	3 months (goitre 1 year)	140/70	N. R., 125, no predom.
98	31	F	?	?	4 years	150/80	N. R, 100, no predom.
99	18	F	None	+	18 months	120/80	N. R., 140, no predom.
100	49	F	None	Not +	1 year (relapse) goitre 12 years	155/85	N. R., 110, no predom.
101	44	F	None	Not +	18 months	—	N. R., 130, no predom.
102	41	F	+ (L.)	?	2½ years	—	N. R., 140, no predom., V. P. Cs., T > P
103	34	M	+ (L. & R.)	Not +	1 year	—	N. R., 90, no predom.
104	20	F	+ (L.)	+	6 months	—	N. R., 130, no predom.
105	27	F	None	?	3 weeks	150/70	N. R., 140–160, no predom., P +
106	38	F	None	Not +	5 years	130/90	N. R., 90, no predom.
107	33	F	None	+	1 year 'always full throat'	165/70	N. R., 125, D. P., R +, P +
108	28	F	None	+	1 year	115/55	N. R., 140, no predom.
109	47	F	None	?	18 months	?	N. R., 115, L. P., T = P
110	32	F	None	Not +	19 months	125/65	N. R., 140, D. P., T +, P +
111	24	F	+ (L. & R.)	+	1 year	175/80	N. R., 140, D. P., T = P
112	56	F	+ (L. & R.)	+	3 years	—	A. F., 120, L. P.
113	47	F	None	Not +	2½ years	160/90	N. R., 120, no predom.
114	68	F	None	Not +	Few months	150/85	N. R., 115, no predom., P +
115	66	M	None	Not +	Many years	—	A. F., L. P., 150
116	63	F	+ (L.)	Not +	14 months	180/110	N. R., 100, L. P. (also P. A. F.)
117	43	F	?	+	18 months	—	N. R., 110, no predom., T +
118	49	F	?	?	1 year	—	N. R., 85, no predom.
119	53	M	+ (L. & R.)	Not +	6 years	—	A. F., 100, D. P.
120	57	M	None	? +	3 years	150/90	N. R., 130, no predom., T +
121	58	F	None	?	3 years	170/85	N. R., 130, V.P.Cs., no predom.
122	49	F	None	Not +	9 months	—	N. R., 110, no predom., P +

TABLE IV (*continued*).

Case No.	Age.	Sex.	Cardiac Enlargement.	Pulmonary Arc.	Duration of Symptoms.	Blood-Pressure.	Electrocardiogram.
123	24	F	None	?	7 weeks	125/75	N. R., 120, L. P.
124	18	F	+(L.)	+	5 years	145/80	N. R., 115, no predom.
125	22	F	None	+	5 weeks	150/100	N. R., 100, L. P.
126	34	F	None	Not +	Few days	145/95	N. R., 110, no predom., P +
127	53	F	None	Not +	4 years	140/70	N. R., 105, no predom.
128	66	F	+(L. & R.)	+	12 years	170/90	N. R., 120, no predom. (also P.A.F.)
129	49	M	+(L. & R.)	?	11 years	—	A. F., 150, no predom.
130	54	F	+(L. & R.)	?	4 years	170/120	N. R., 130, L. P., aur. P. Cs.

Though not invariably, diminution of the heart-size has been described after operation; but changes in the transverse diameter can only be accepted as evidence of alteration in the size of the heart if changes in body-weight and in the position of the diaphragm are both taken into account. In eleven cases records were taken just before thyroidectomy and again at periods of one to three months after the operation. Of four with fibrillation *before* and resumption of normal rhythm *after* operation, in two there was a decrease of the transverse diameter by 1·25 cm. and 1·2 cm. respectively, in spite of an increase in body-weight. In one case where fibrillation had been present for only a short time before operation, and where the heart was not enlarged, there was an increase in the transverse diameter after operation. In the remaining case, normal rhythm was not restored (the patient had an idiosyncrasy to quinidine), and the heart was the same size several months after operation. In seven cases with normal rhythm enlargement was present before operation in four; in two of them the transverse diameter was reduced by 1·5 cm. and 0·8 cm. after operation in spite of a gain of body-weight of 16 lb. in each. In the other two cases there was an increase of 1·8 cm. and 1·1 cm. respectively, and both patients had gained considerably in weight.

Thus no rule seems to govern the direction of alteration in this diameter of the heart after operation. The matter is a complex one in which many factors are concerned, some of which tend to broaden the heart-shadow, while others have the opposite effect. Increase in body-weight tends to raise the diaphragm and so to extend the transverse diameter. When failure subsides or the rhythm becomes normal, lowering of the diaphragm follows a shrinking liver and reduced abdominal distension, so that the transverse diameter is diminished. In view of these difficulties and the scantiness of our material we can draw no conclusions as to actual changes in heart-size from our observations on changes in the transverse diameter after operation.

The pulmonary arc. As early as 1913 it was stated by Bauer and Helm (5) that prominence of that arc on the left border of the heart-shadow which is formed by the pulmonary artery was sometimes a feature of thyroid heart disease; and although from time to time since mentioned, it has often found no place in descriptions of the heart in goitre. Rösler (52), however, has recently drawn attention to it.

We have especially studied this feature, and find that while in some the pulmonary arc may present so striking a prominence as strongly to suggest mitral stenosis, in other cases, where the heart has been considerably affected as shown by increase in size, the pulmonary arc has appeared unchanged. Yet this absence of change may be more apparent than real; for prominence of this arc is largely judged by its relation to the neighbouring arcs, namely, the aortic above, and the left ventricular below. In the normal heart this contour is concave (Pl. 25, Fig. 1), flat (Pl. 25, Fig. 2), or slightly convex. The last form is seen especially in the long narrow type of thorax. When the normal heart happens to lie to the left, the pulmonary arc tends to be prominent, and this is especially well seen in the funnel-chest. As in the diagnosis of enlargement of the heart as a whole, inspection of the records has been the first method used in classifying the pulmonary arc as prominent or not. Using this method a definite prominence was found in forty-two instances; it was doubtful in an additional thirty; in fifty-eight the pulmonary arc appeared normal. A change in the pulmonary arc is often seen at an early stage in goitre heart, and preceding any enlargement of the heart chambers. Over a third of the cases showing such a change had hearts of normal size.

Measurements have been applied to this arc by Vaquez and Bordet (60), who measure the perpendicular distance from the mid-point of the pulmonary arc to the mid-sternal line. Abreu (1) measures the 'rise' or *flèche* of the arc (see the line *AB* in Pl. 26, Fig. 4). He gives a normal for this distance of from 1–3 mm.; if it should be between 3 and 5 mm. a lengthening or dilatation of the pulmonary artery is probable, and if more than 5 mm., certain. Measurement of the 'rise' is, however, frequently useless as an indication of increase in the projection of this arc for the reason already given, viz. that this depends to a large extent on the development of the neighbouring contours. If the left ventricular contour is displaced outwards, or if the aortic arc is prominent, an undue projection of the pulmonary arc is thereby concealed. Its contour may be quite flat, or even slightly concave, and yet the pulmonary artery may be abnormally large. Pl. 27, Fig. 5, shows a heart with definite prominence of the pulmonary arc; Pl. 27, Fig. 6, shows a teleradiogram taken seven months later; during this period auricular fibrillation had been present, and the patient's weight had increased, factors likely to broaden the heart-shadow. A definite increase in the heart-width has in fact occurred, and the right and left borders have extended laterally. The effect of the change in the left ventricular contour has been to conceal the convexity of the pulmonary arc, which now appears as a straight line. In another instance the pulmonary arc was slightly concave in the

orthodiagram, yet at necropsy the pulmonary artery was found to be abnormally wide.

The rise of the arc was measured in the forty-two cases judged to be abnormal by inspection. In seven it was 5 mm. or over, in eighteen it was between 3 and 5 mm., and in seventeen less than 3 mm.

The length of the arc, that is the extent to which it participates in the left border of the heart, is frequently increased. No figures are given in the literature as to the normal length of this arc, but we believe from inspection that it is often appreciably increased in goitre heart. The chord of the arc (line *CD* in Pl. 26, Fig. 4) was measured in fifty-one cases, and found to have an average length of 56 mm. There were two teleradiograms in which the conus arteriosus could be seen as a separate convexity on the left profile, smaller than, and situated below, that of the pulmonary artery. A similar appearance is often seen in mitral stenosis, though here it is more common for the convexity of the conus to merge with or exceed that of the pulmonary artery. That the conus is taking a part in producing the 'pulmonary' arc can be inferred if the arc extends to a very low level. This appearance was never seen in our goitre cases. A pulmonary arc prominent in the antero-posterior view may be seen equally well or even better in the first oblique position, with the patient rotated about 30° to his left. In this position will be noted the straight posterior heart-border separated by a clear space from the vertebral column, from which it may be inferred that the left auricle is not enlarged. Routine examination of our cases has never revealed a large left auricle, an important distinction of the goitre heart from that of mitral stenosis. Thus, while the heart may sometimes present a similar appearance in the antero-posterior view in the two conditions, the disclosure of a large left auricle in the oblique view will almost compel a diagnosis of mitral stenosis.

The vascular pedicle. The pedicle of the heart may be modified by changes in its normal constituents—the aortic arch and its branches, and the superior vena cava—or by the presence of a retrosternal goitre. In the normal chest the right border of the pedicle is probably formed by the superior vena cava, and the shadow of the ascending aorta lies mesial to it. In goitre the vena cava may be unduly prominent, being often seen as a faint shadow with a definite straight border pulsating slightly or not at all, and situated to the right of the distinct and denser aortic shadow (see Pl. 28, Fig. 7, of which Pl. 28, Fig. 8 is an explanatory outline drawing). Congestive heart failure is not necessarily present when this phenomenon is observed.

The aorta itself is often abnormal in the height of its arch when judged by its relation to the lower border of the sternal ends of the clavicles. Vaquez and Bordet (60) state that the normal distance between the highest level of the arch and the lower border of the clavicles is 20–30 mm. There is no doubt, however, that the arch-clavicle distance may be very much less than this in health, and Abreu (1) affirms that it may be as little as 2–4 mm. In the hypersthenic type with a broad chest and high diaphragm such small measure-

ments will not necessarily indicate any aortic change, nor will they do so where there is such great enlargement of the heart that its base (and with it the origin of the aorta) is raised. But where the chest is of average or narrow shape, and where the heart is not grossly enlarged, a small arch-clavicle distance is probably indicative of lengthening of the aorta, and where the arch attains or rises above the lower border of the clavicle this is almost certain.

In our series there were thirty-eight cases which came into this last category, their average age being thirty-eight years, and the average blood-pressure in twenty-five (in the remainder there was either no record of the pressure, or it could not be taken because of the presence of fibrillation) being 150 systolic and 74 diastolic.

There were eight cases with an arch-clavicle measurement of 1 to 4 mm. Excluding four on account either of a broad chest or of auricular fibrillation, the average blood-pressure in these was 149 systolic and 91 diastolic, and the average age was twenty-six years. Although an increase of the height of the aortic arch was so frequently seen, undue prominence of knuckle and of the ascending portion of the arch was conspicuously absent, a contrast with other conditions which lead to an elevation of the arch such as primary hypertension and atheroma. Excluding one case with a blood-pressure of 190/115 and one with arteriosclerosis, there were two only with a prominent knuckle and three with a prominent ascending arch.

The pedicle is sometimes modified by a retrosternal goitre. The aortic knuckle may be displaced to the left so that it becomes very prominent as if from severe atheroma (see Pl. 29, Fig. 10), or the shadow of the goitre may be superimposed on that of the aorta so that an aneurysm is simulated. The diagnosis has also to be made from mediastinal neoplasm, and from oesophageal pouch. An uncommon condition of which several examples have recently been reported is an accessory azygos lobe of the right lung (7), (37), (38), (40). When this lobe, which is very variable in size, is no more than a thin strip situated at the mesial aspect of the right apex, it may be collapsed, and in its paratracheal site may suggest a retrosternal goitre.

Correlation of pulmonary and aortic changes. In twenty-three cases changes in the appearance of the pulmonary artery co-existed with some change in the aorta. In sixteen a high arch was associated with a prominent pulmonary arc, and in one other there was in addition prominence of the ascending aorta. In five the pulmonary change was associated with a prominent ascending aorta but without an abnormally high arch, and in one (a woman of 36) with a prominent aortic knuckle.

Pulsation. In our whole clinical series the heart-rate was nearly always over 100 a minute. On the fluorescent screen the rapid movement of the left ventricular and (to a less extent) the right auricular border is well seen. Rösler (52) states that the systolic movement is greater and speedier than in a normal heart beating at the same rate. This we have been unable to discern. On the other hand, the excursions of the pulmonary arc and the aortic knuckle

are conspicuously increased, more especially that of the former. These remarks apply only to patients with active thyrotoxicosis; if this be absent at the time of examination, pulsation will not be excessive.

Electrocardiogram. Electrocardiograms were taken of 124 of the patients. The individual records showed nothing that has not already been reported. Tachycardia with normal rhythm was most frequent; occasionally there were ventricular ectopic beats (in one auricular) occuring at rapid heart-rates. Auricular fibrillation was recorded thirty-four times (27 per cent.) and auricular flutter once. The P wave was of large amplitude, i.e. 3 mm. or more in thirty-three patients with normal rhythm (37 per cent.). Less frequently the amplitude of the T wave, between which and the increase of the basal metabolic rate White and Aub (63) found a very limited parallelism, was too great.

Ventricular predominance. When R_2 was of greater amplitude than R_1 and R_3, a curve was considered to show no predominance. A curve in which R_1 was of greater amplitude than R_2, or where R_1 and R_2 were equal and S was the largest deflexion of QRS, was considered to show predominance of the laevogram. Similarly predominance of the dextrogram was assumed where R_3 exceeded R_2, or where R_3 and R_2 were equal and S was the largest deflexion of QRS_1.

By these criteria 77 curves showed no predominance. Of these 77 patients, 29 had enlargement of the heart, great in 8, moderate in 7, and slight in 14. There were 33 with predominance of the laevogram. In 18 the heart was enlarged; in 6 it was greatly so, in 10 moderately, and in 2 slightly. Thirteen records showed predominance of the dextrogram; 8 of these patients had enlargement of the heart; in 2 it was great, and in 6 slight. These results are tabulated below.

*Electrocardiograms (124 cases).**

(1) No predominance	77 cases		
Enlargement of the heart in	29 „	great in 8 moderate in 7 slight in 14	
(2) Predominance of laevogram	33 „		
Enlargement of the heart in	18 „	great in 6 moderate in 10 slight in 2	
(3) Predominance of dextrogram	13 „		
Enlargement of the heart in	8 „	great in 2 slight in 6	

* One excluded on account of bundle-branch block.

Can any inference be drawn as to the relative degree of hypertrophy in the two ventricles from the nature and frequency of ventricular predominance, or its absence, in these records? Herrmann and Wilson (34) showed that, as their relative weight was but one of several factors influencing the form of the ventricular complex, its effect only prevails when the ventricular weight is considerably increased. We can infer nothing therefore from those curves taken in cases of slight or moderate enlargement. Of those with considerable

enlargement, 16 in number, the electrocardiograms would suggest an equal increase in the two ventricles in 8, more in the left in 6, and more in the right in 2.

Discussion.

A. *Pathological.* In the reported post-mortem observations on the heart in goitre, there is general agreement that the heart is often but not always enlarged. Fahr and Kuhle (22) found some macroscopic change, hypertrophy, dilatation or cloudy changes, in fifteen out of eighteen cases with Basedow's disease, and without exception in eight cases of colloid goitre with cardiac symptoms. Willius, Boothby, and Wilson (65) considered hypertrophy to be present in sixteen of a series of twenty-one. Although this was undoubted in two, an increase of only 5–10 per cent. in the heart-weights of the remainder does not clearly indicate enlargement unless the patients were wasted. Wilson (66) quotes a fatal case of goitre with a history of symptoms for four years, and heart failure for two months, where the ventricular body-weight quotient was normal, as showing that hypertrophy is not invariable. He admits that cardiac enlargement as seen radiographically is one of the most important complications of goitre, but thinks that it is due chiefly to dilatation. Symmers (56) described six cases of marked hypertrophy which he believed to be of goitrous origin, but coronary disease and high blood-pressure are not clearly excluded in three, and in two others there was rheumatic heart disease and syphilis respectively. Of other observers who report cardiac enlargement *post mortem* we may mention Loos (47), Jaksch and Rotsky (39), and Thomas (57). Cabot (14) appears to stand alone in denying that the heart may be hypertrophied and dilated as a result of goitre; yet he gives the heart-weights in two of his cases as 365 and 285 gm., the body-weights not being mentioned.

Experimental work on the question of hypertrophy clearly shows a relation between thyroid disease and increase in the heart-size. Simmonds and Brandes (54) fed ten dogs with 10 grm. of thyroid extract daily for periods up to 100 days. At necropsy they found a heart-weight—final body-weight ratio, not only much greater than that for normal dogs, but considerably greater than that for starved dogs, except when wasting was extreme (over 36 per cent.). The heart then loses what it has gained in hypertrophy and the ratios obtained approximate to those of simple inanition. The hypertrophy affected all chambers of the heart, but the proportional increase in the left ventricle was slightly greater (about 6 per cent.).

The histological findings in the heart-muscle of patients dying of goitre are often slight, and some authors doubt if they are more than may be found in any heart coming into the same age group (65). Goodpasture (25), however, found an acute necrosis of the muscle similar to that associated with the extreme intoxication of acute fevers; and his experimental work leads him to the conclusion that these changes are the result of a terminal injury by agents normally without effect on the heart-muscle, but which are capable of severely damaging

a heart rendered susceptible by the thyroid. In an experimental inquiry by Hashimoto (33) histological appearances very similar to those described by Aschoff in the rheumatic heart were found. Some abnormal microscopic finding was present in nearly all of a group reported by Fahr and Kuhle (22) and chosen because of cardiac symptoms.

Our findings in forty-three necropsies show clearly that in about 50 per cent. of goitre cases coming to necropsy there was cardiac enlargement. This was usually general in distribution, though it might involve the left ventricle only, or in a few the left ventricle more than the right. Only once was the right heart predominantly affected, and then there was coincident rheumatic heart disease. The average age was distinctly higher in those with hypertrophy than in those without, yet the group does include some young people. It is certain that hypertrophy may occur in a young individual from goitre in the absence of auricular fibrillation and of heart failure. The average duration of symptoms was also longer in those with enlarged hearts, namely 1·9 years, as compared with 1·3 years in those without enlargement.

There are striking differences between those goitre patients with established auricular fibrillation and those who retain normal rhythm. Patients dying with this arrhythmia were nearly twice as old as those who died with normal rhythm or terminal fibrillation, and the heart-weight was appreciably greater.

B. *Clinical and radiological.* The history of our knowledge of the heart in goitre falls naturally into two periods: one preceding, and the other following the appreciation of the thyroid as a cause of auricular fibrillation. Early accounts of the X-ray picture were given by German authors, especially of the type in which the heart was enlarged mainly to the right. This, the 'pneumo-mechanical' heart, was thought to result from an embarrassment of the right heart due to tracheal pressure. But other forms were soon recognized; and Blauel, Müller, and Schlayer (10) spoke of a toxic type in which the increase was of the left half of the heart, in four of eleven such cases. Otten (49) writing in 1912 stated that the goitre heart scarcely deviated from the normal in size, but that the shape was altered so that it became more globular. This resulted from a rounding of the left ventricular profile, and a vaulting of the left middle arc, the last ascribed by Otten to a prominence of the left auricle. He also noted undue prominence of the superior vena cava. A year later Bauer and Helm (5) confirmed the fullness of the left middle arc, but ascribed it correctly to enlargement of the pulmonary artery. These authors found the upper normal limits for heart-size were not exceeded, as shown by teleradiograms, but hypertrophy was suggested to them by a rounded apex. They noticed that the aorta was often high though perhaps small, and that the pulsation of the whole of the left border, especially of the pulmonary arc, was excessive. Vaquez and Bordet (59) described globular enlargement of the heart, and thought its wall unduly flaccid. Dietlen (19) in 1923 stated that in goitre with heart changes the left ventricle was involved first. He also found the superior vena cava prominent, but made no distinction between the amplitude

of the systolic contractions in goitre and that in tachycardia from other causes. Baumgartner and others (6) described three cases of goitre with fibrillation; they mentioned bilateral heart enlargement, and once a 'marked prominence of the auricular curve suggesting mitral disease'. An interesting study was made by Coller (15) on 500 cases of goitre. He grouped them into age decades, and found an elevation of the basal metabolic rate from nil in the second decade to +32 per cent. in the fifth decade. Similarly the proportion with enlarged hearts rose from 18 per cent. in the third to 50 per cent. in the sixth decade.

Kerr and Hensel's (41) observations showed them a heart generally enlarged to the left in goitre, with prominence of the pulmonary arc; in some they found widening of the pedicle. Wilson in 1924 (66), and Bickel (8), (9) believed the heart to present a globular enlargement. Bickel gave a detailed account of the close similarity between the clinical signs and the electrocardiograms of goitre and mitral stenosis, but failed to note the similarities and differences of the radiographic picture. Assmann (3) stated that the orthodiagram usually shows a heart of normal size in the early stages, and that later there is often considerable enlargement. The experience of Smith and Colvin (55) in dealing with several hundred cases was exceptional in that any degree of cardiac enlargement was unusual on X-ray examination. The impression of Hurxthal (36) gained from teleradiograms was similar; he found hypertrophy to be rare except in a certain group of cases, and in these he ascribed it to co-existing cardiovascular disease. He concluded that goitre does not injure the normal healthy heart. Hurxthal, Menard, and Bogan (36 a) in 1930 reached similar conclusions after comparing the size of the heart in toxic goitre with that in non-toxic goitre. They said that if hyperthyroidism causes enlargement or hypertrophy and dilatation, it is slight. The form of the heart was not specially considered. Rösler (52) in 1928 gave a description of what he believes to be a characteristic picture of the heart in goitre. He found no departure from the normal size in a large proportion. The type of pulsation to him is peculiar; the contraction of systole is said to occur more quickly than in a normal heart beating at the same rate. He mentions a prominent long pulmonary arc, and a broad rectilinear superior vena cava. Lahey and Hamilton (42) in 1924, and Lahey (43) again in 1930, expressed the opinion that in young individuals with previously undamaged hearts there are no cardiac changes in goitre. According to Lahey, when failure occurs in goitre it is due to the effect of the thyroid on a previously damaged heart.

The importance of goitre as a cause of auricular fibrillation, although their association is almost recognizable in Parry's original description, has only been appreciated in the last few years. It is in connexion with this arrhythmia that what has been termed 'masked hyperthyroidism' is of great importance. We now know that goitre can cause fibrillation, especially in a middle-aged or elderly individual, without the classical signs of intoxication. Visible enlargement of the gland may be slight or absent; no eye changes may be seen, or at

the most a slightly staring expression; the nutrition may be fully maintained and the basal metabolism need not necessarily be at all raised (29, 30, 45, 51, 58, 64). We describe three examples of this condition in our post-mortem series (Cases 38–40). One probably and another certainly had fibrillation. The third, a young woman, had no symptoms to suggest thyroid intoxication, yet at necropsy a considerable enlargement of the heart was discovered. Coller (15) studying 500 patients with goitre never encountered fibrillation between the ages of 20 and 40, but in the sixth decade found its incidence as high as 30 per cent. Other observers (16, 35, 65) report an incidence, irrespective of age, of 10–23 per cent.

Heart failure in goitre has been discussed by Andrus (2), Hurxthal (36), Dameshek (16), and Lahey (43). It is agreed that this is associated in the majority with fibrillation, but the proportion varies with the author from just over 50 to 90 per cent.

The literature on the blood-pressure in goitre suggests that the systolic is slightly raised, while the diastolic remains stationary or a little lowered, leading to an increase in the pulse-pressure (12, 16, 23, 44, 55, 65). Boas and Shapiro (11) reported a small series of cases with diastolic hypertension which they believed to be a result of thyroid disease.

Our own X-ray observations have given us reason to believe that when the symptoms of goitre are mild and of short duration the heart is likely to be normal in size and shape. Apart from these, and especially in older people, changes in both respects are frequent. Moreover the X-ray picture is at times distinctive, and a diagnosis becomes almost possible from this alone.

In nearly one half of the 130 patients examined there was an appreciable enlargement of the corrected heart-shadow. This involved the shadow to the right and to the left of the middle line, thereby producing in a majority of cases a globular enlargement. Occasionally the left side appeared to be alone affected. Usually the increase was slight or quite moderate. Considerable increase was not rare, however, and apart from patients with associated hypertension, i.e. those showing an increase in both systolic and diastolic pressures, it was always accompanied by auricular fibrillation and often by heart failure. In these more extreme examples of enlargement the extension of the left side of the heart was always much greater than that of the right. The main factors which appeared to determine the size of the heart were the age of the patient, the duration of symptoms and their severity, and the presence of fibrillation and failure. Gross enlargement was never seen under the age of 30; but we cannot agree with those observers who find no heart changes in the young, and who question the power of the thyroid to damage a previously normal heart. We repeatedly found enlargement in goitre patients under 30, and our post-mortem records furnish proof that at any age the thyroid may induce cardiac hypertrophy. We are not especially concerned with the pathogenesis of this change; but considering the increased consumption of oxygen which the condition entails, and the fact that the arteriovenous oxygen difference is not increased

(13), (24), and that in some instances there is the added burden of anaemia, some responsive development of the cardiac muscle is not surprising. Lewis and Drury (46) suggest that the cardiac hypertrophy of arteriovenous aneurysm may depend on a reduced coronary flow brought about by a high pulse-pressure. Similarly the high pulse-pressure observed in goitre cases may perhaps play some part, even if slight, in bringing about hypertrophy.

Undue prominence of the pulmonary arc of the heart outline was discovered in about one-third of the cases (Pl. 26, Fig. 3 and Pl. 27, Fig. 5). In a further group, amounting to about one-sixth of the total, there was a suggestion of this; but as there are fairly wide variations of this arc within normal limits, they were not accepted as pathological. This prominence is also seen in certain other conditions, but it is otherwise rare apart from mitral stenosis and congenital heart disease.

The shape of the arc may be altered in goitre exactly as in mitral stenosis, but, as already mentioned, in the valvular disease the conus of the right ventricle often leads to bulging of the lower part of this arc to a degree not seen in goitre. Changes in the pulmonary arc are often visible at an early stage of goitre and before any alteration of the heart-size. In sixteen cases the heart appeared entirely normal apart from this prominence, which represents a dilatation of the pulmonary artery. In comparison with the aorta this vessel is thin-walled and feebly resistant to an increase of pressure within it, and it is not improbable that it will dilate under the strain of an increased pulse-pressure and increased heart-rate. We have measured the lumen of the aorta and pulmonary artery at necropsy in six cases of goitre, and the results are given in the following table.

Observation.	Circumference of Pulmonary Artery.	Circumference of Aorta.
	cm.	cm.
1	7·5	6·7
2	6·5	5·1
3	9·0	8·0
4	7·2	6·2
5	7·2	6·0
6	7·8	6·7

Walmsley (61) gives the circumferences of the normal aortic orifice as 70–81 mm. in the male, and 64–76 mm. in the female. The circumference of the pulmonary artery he gives as 72–91 mm. in the male and 66–89 mm. in the female. This furnishes an average measurement for the pulmonary artery of about 8 per cent. greater than that of the aorta. Our measurements on goitre cases made at the level of the upper margin of the cusps on the opened vessels, show a 17 per cent. difference in favour of the pulmonary vessel, which suggests that it has undergone dilatation.

In the vessels of the pedicle proper, an increase in the height of the aorta is the most frequent change. The arch was found to be abnormally high in about one-third of the cases. The knuckle was not found to be prominent, but it was never unduly small as it so often is in mitral stenosis. The shadow of the

superior vena cava was conspicuous in a few cases, the congestion of failure explaining this in some, but not in all. In these others there are probably several factors concerned; we may mention deviation laterally of the cervical vessels by the enlarged thyroid, and fullness of the vein due to excessive venous return from the thyroid.

There is a certain negative finding in the heart which must not be omitted, for it is valuable in differential diagnosis from mitral stenosis. This is the absence of enlargement of the left auricle revealed when the patient assumes the left turn or first oblique position. The absence of any posterior extension of this chamber is most certainly noticed when the oesophagus is rendered visible with barium. The swallowed barium then shows that the course of the oesophagus is almost straight as it passes behind the heart. Only exceptionally is the oesophagus displaced by the goitre heart; the heart is then greatly enlarged as a whole and the deviation does not imply a particular increase in the size of the left auricle.

The special features of the goitre heart have been described individually, but we may go further and distinguish a combination of these which is characteristic and on occasion diagnostic. We refer to a heart outline which shows enlargement to the left combined with a prominence of the pulmonary arc. The aortic knob is normal, neither prominent nor unduly small. Together these changes produce an almost straight left heart-border from aortic knob to apex. Yet the right auricular arc is only slightly or moderately prominent (Pl. 28, Figs. 7 and 8); and when the patient is rotated half to his left, no special fullness of the left auricle is visible.

Summary.

A consecutive series of 130 patients with goitre causing symptoms was examined with the primary object of deciding the size and shape of the heart by radiography. In addition a series of post-mortem records of 43 goitre cases was investigated to determine the incidence and distribution of cardiac hypertrophy.

Post-mortem series. Of the forty-three cases of goitre all but three had shown the classical symptoms of thyroid intoxication. There proved to be hypertrophy of the heart in rather more than one-half. The increase involved both ventricles as a rule, sometimes the left, more than the right, occasionally the left alone. A predominant or isolated hypertrophy of the right side was never seen. In general it was the younger patients and those with the shorter duration of symptoms who showed no hypertrophy. It was also in the younger patients, say under 30, that the rhythm had been normal throughout or fibrillation had come only as a terminal event.

Established fibrillation occurred in older people with an average age in eight cases at death of 51 years. The heart-weight was greater on the average in those with established fibrillation than in those with normal rhythm. The greatest increase in heart-weight was registered in those with fibrillation and

heart failure. When emaciation was extreme, the heart was only slightly or not at all hypertrophied. In the three cases of goitre where the gland had not been suspected of producing symptoms, there was cardiac hypertrophy in two, and perhaps in the third.

Clinical series. Clinical and X-ray observations were made on 130 patients with goitre and symptoms from it. Without X-ray examination it is difficult to determine the size of the heart, especially when there is tachycardia, and either a teleradiogram or an orthodiagram or both were taken of every patient. The criteria of enlargement applied to these records are discussed. We found enlargement in about 45 per cent. of cases, usually slight or quite moderate, but not rarely great. In most it involved both contours of the heart, but more particularly the left, and sometimes the left only. Although several cases with striking displacement and some stenosis of the trachea were included, enlargement of the right side of the heart alone was never seen. Electrocardiograms, so far as they can be used as an indication of hypertrophy and its relative distribution, confirmed the radiographic and post-mortem findings.

The incidence of auricular fibrillation, including both paroxysmal and established forms, was 27 per cent. Heart failure was present at some time in twelve, and all these had fibrillation, except one with a complicating hypertension.

A few serial records showing progressive increase in the heart-size were obtained, all from patients with permanent fibrillation. Comparison between records taken before and after thyroidectomy was made in eleven cases and gave variable results—there might be no change, an increase, or a decrease in the transverse diameter of the heart. After operation several factors come into play which render it difficult to accept the changes as evidence of actual alteration in heart-size.

The form of the heart is often affected in a characteristic way in goitre. Undue prominence of the pulmonary arc was a striking feature of about one third of the series, sometimes appearing as a convexity on the left profile, sometimes combining with an enlargement of the heart to the left to render this profile straight. An exaggeration of this arc is often an early change, preceding any enlargement of the heart chambers. Post-mortem measurements showed that the pulmonary artery was often dilated.

The left auricle was not enlarged out of proportion to that of other chambers of the heart—a sharp distinction from the heart of mitral stenosis. The superior vena cava was sometimes prominent; this would be expected with the venous congestion of heart failure, but such an explanation only applied to a small proportion. The aortic arch reached too high a level in the chest in about one-third. The form of the vascular pedicle was modified occasionally by a retrosternal goitre.

When symptoms are mild or of short duration the heart in goitre is normal in size and shape. When symptoms are severe and of long standing it is in a fair proportion both enlarged and modified in shape. The greatest enlargement

is seen with auricular fibrillation and failure. The special form characteristic of the goitre heart is based upon a combination of prominence of the pulmonary arc, of the left ventricle, and to a minor extent of the right auricle. As a result of these changes, the heart may be generally enlarged, the contour retaining much the same shape as in the normal heart (see Pl. 27, Fig. 5), whereas almost all other forms of cardiac disease causing enlargement greatly modify the shape. In their fully-developed form changes in the left arcs produce a distinctive picture with its straight left border and a right auricular arc only slightly enlarged. The heart so disposed, when seen from in front, has some resemblance to a ham (Pl. 28, Figs. 7 and 8). This picture differs from that of mitral stenosis in the relatively slight prominence of the right auricle and the fuller aortic knuckle as seen from the front, and in the absence of left auricular enlargement as seen in the first oblique position. It approximates more to the cardiac outline of combined mitral stenosis and aortic incompetence.

Radiological examination is a help in judging the presence or severity of a cardiac lesion in a patient with goitre.

The demonstration of cardiac enlargement is important from the standpoint of the surgical treatment of goitre. When present, it is an added reason for, rather than a contra-indication to, surgical treatment. Though the greater the enlargement, the poorer is the prospect of a complete return to normal, yet the aid of surgery will often be required to check the progress of the lesion.

In deciding the cause of obscure cardiac symptoms or enlargement, or of auricular fibrillation with or without failure, the discovery of the characteristic radiographic picture may suggest a goitrous aetiology.

We wish to thank the Staff of the London Hospital for their co-operation. The work by one of us (H. C.) has been done under the tenure of the Paterson bequest.

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DESCRIPTION OF PLATES.

PLATE 25, FIG. 1. Teleradiogram of normal heart with slight concavity of pulmonary arc.

FIG. 2. Teleradiogram of normal heart with straight pulmonary arc. Man, aged 25.

PLATE 26, FIG. 3. Teleradiogram from a woman of 23, with goitre, simple tachycardia, and slight exophthalmos; one year's duration. The pulmonary arc is prominent and elongated; the ventricle is slightly enlarged to the left.

FIG. 4. Orthodiagram from a man of 56, with goitre, partly substernal, showing slight general enlargement, and lengthening (C–D), and prominence of the pulmonary arc B. A–B is the rise of the arc. F–E shows the distance of the arch of the aorta from the clavicle.

PLATE 27, FIG. 5. Teleradiogram from the same case as Fig. 4, showing slight bilateral enlargement of the heart and prominent pulmonary arc. The shadow of the retrosternal goitre is shown below the inner ends of the clavicles.

FIG. 6. Teleradiogram from the same case as Figs. 4 and 5 taken seven months later, and one month after the onset of auricular fibrillation. The heart is larger, and this makes the pulmonary arc seem less prominent though it is still elongated.

PLATE 28, FIG. 7. Teleradiogram from woman aged 20 with exophthalmic goitre of six months' duration, showing enlargement of the heart, especially to the left, a prominent pulmonary arc, and a high aorta. The edge of the superior vena cava is seen on the right.

FIG. 8. Outline of teleradiogram taken from the same case as Fig. 7, showing certain characteristics of the goitre heart. The superior vena cava (S. V. C.) is prominent. The right auricular contour (R. A.) is full. The aortic knuckle (A. K.) is high. The pulmonary arc (P. A.) is filled in, and the left ventricle (L. V.) extends too far to the left, so that the whole left border is straightened.

PLATE 29, FIG. 9. Teleradiogram from a man of 60, with auricular fibrillation of a year's duration and recent congestive failure. Small goitre, tremor, wasting, and exophthalmos. The figure shows much enlargement of the heart to right and left.

FIG. 10. Teleradiogram from a man of 56, with substernal goitre, which displaces the aortic knuckle to the left. The heart is enlarged.

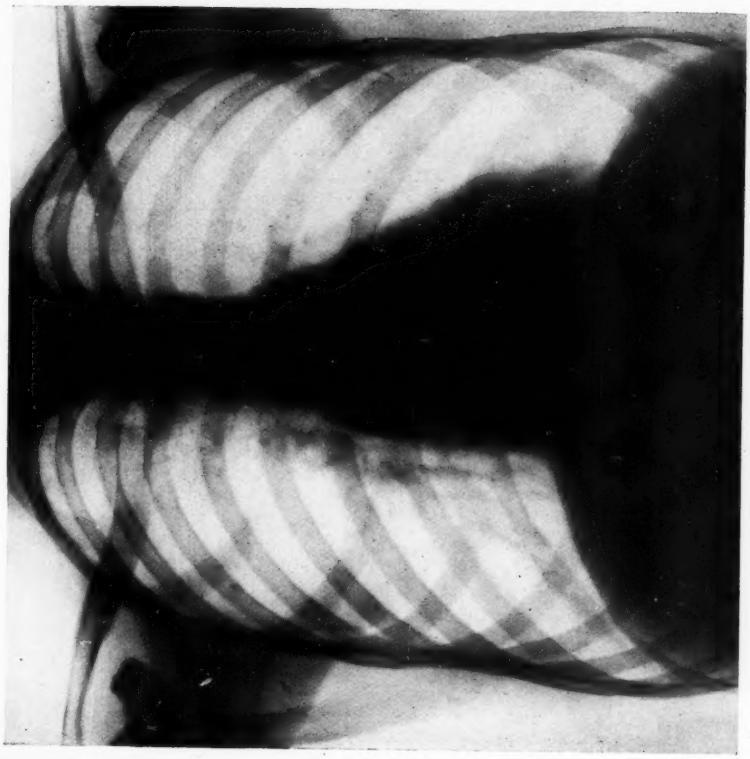


FIG. 2

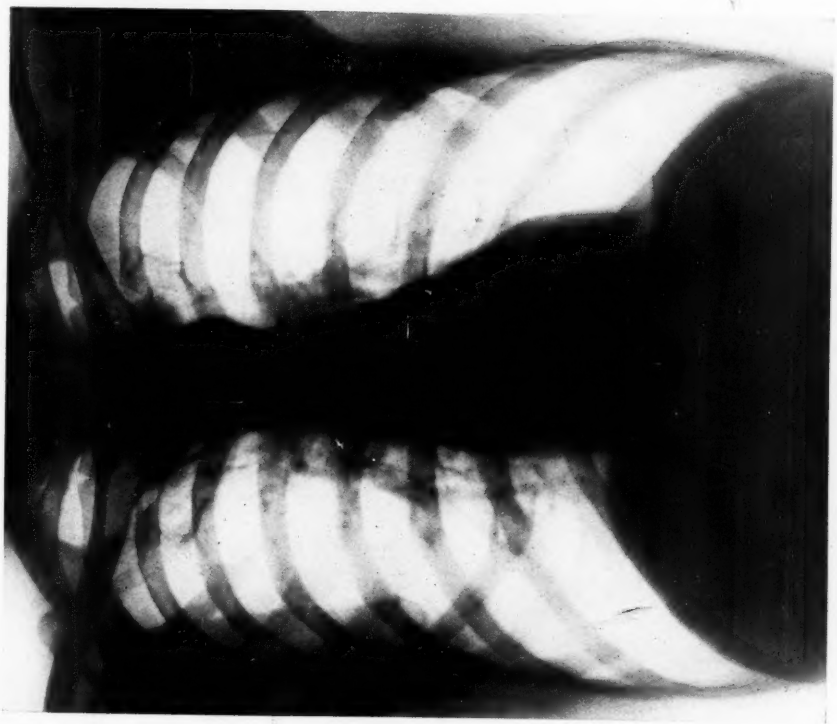


FIG. 1

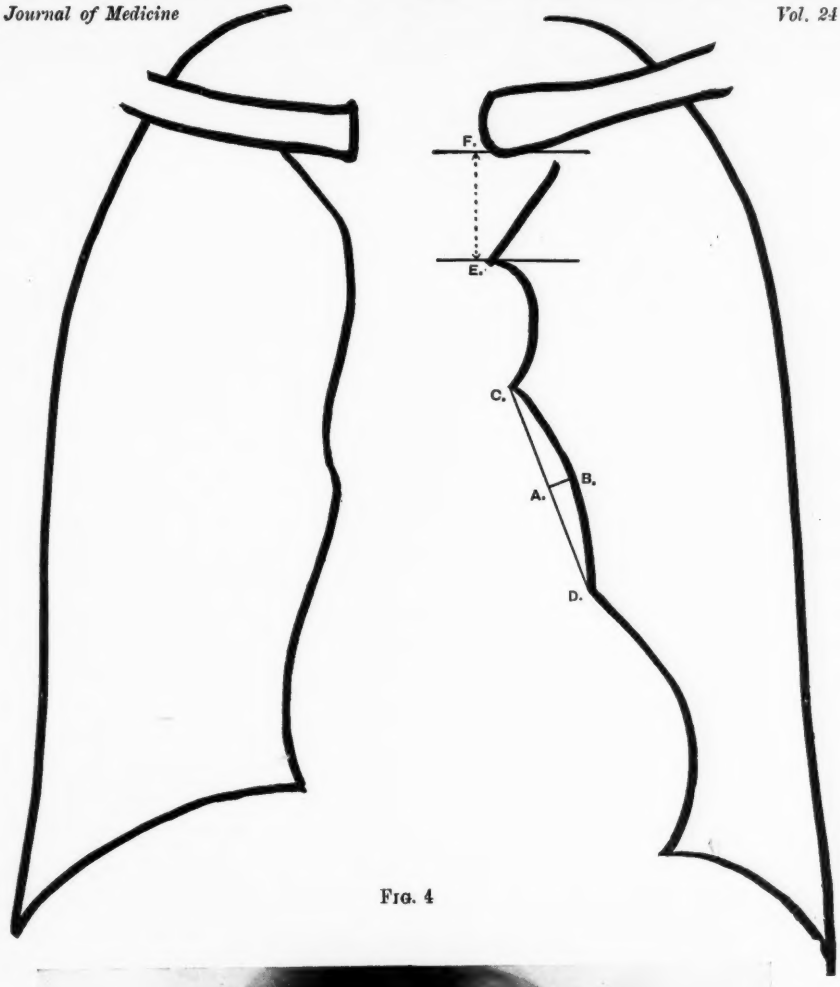


FIG. 4

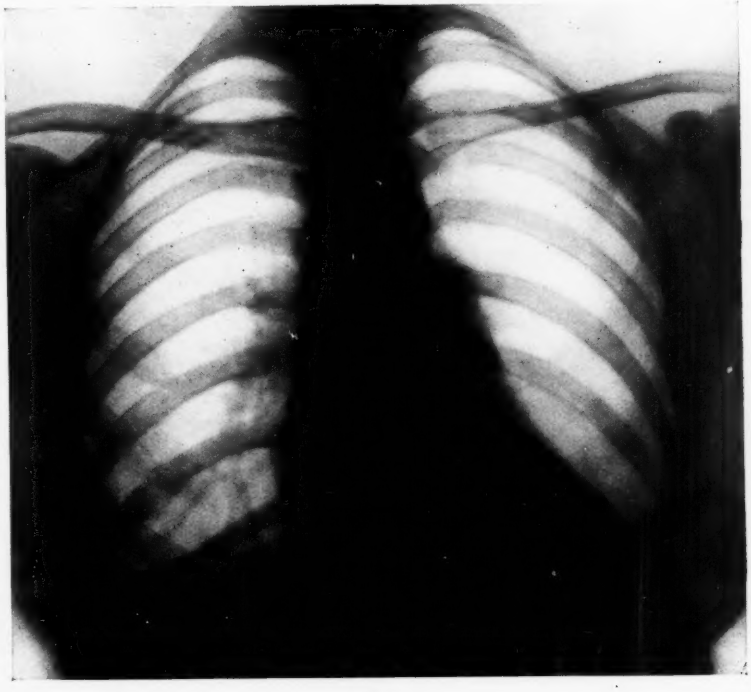


FIG. 3

616.348 : 616—008.

FUNCTIONAL DISORDERS OF THE COLON[1][2]

By EDMUND I. SPRIGGS

With Plates 30–34.

I. *Introduction.*

For knowledge of the diseases of the colon the profession owes much to Sir William Hale-White, whose papers from 1888 onward classified these disorders, with clinical descriptions that have not been surpassed. The writings of T. Boas, R. Hutchison, A. F. Hurst, Jacquet, and Mathieu and Roux should also be mentioned; and especially a paper by Lord Dawson in 1921: also in Canada the writings of Goldie, Hamilton, and Thorlakson. Among recent papers upon the functional disorders of the large gut are those of Ryle and Tidy in England, Bastedo, Kantor, and Jordan and Kiefer in the United States, Gählinger and Bécart, and Chiray and Stieffel in France.

Incidence of diseases of colon. Some major or minor disorder of the colon was noted on clinical, faecal, or radiological evidence in 2,086 out of 4,000 cases under the writer's care, in which an investigation of the body generally was made, classified from the Ruthin Castle records by Dr. Mary Watson. In the greater number of these cases the diagnoses as regards the patients were widely various, the main disease lying in some other organ or system, and the state of the colon, especially under the headings of colic delay and disorder of tone or position, being a complication or accompaniment. The list includes, however, all the patients with symptoms referable to the colon, except those with simple delay only, and those whose clinical state precluded such examinations as that of the alimentary canal with X-rays, e.g. cases of severe ulcerative colitis, acute appendicitis, and the like.

The table on the following page shows the distribution of the lesions or disorders.

The classification can be taken as accurate, except in one or two minor matters. For example, as the years go by the view of the clinician as to what is worth recording alters, and to some extent also the terminology. Thus, our present standard of what shall be called a 'dropped' colon (p. 550) was not established in the earlier period corresponding to the first 20 per cent. of the cases.

[1] Received October 30, 1930.

[2] An address opening the discussion on this subject at the Meeting of the British Medical Association at Winnipeg in August, 1930, was founded upon the data here recorded.

Redundancy, again, is recorded mostly in the later cases, and was therefore present more often than the figures show.

TABLE I.

Distribution of Lesions or Disorders of the Colon noted in 4,000 Consecutive Cases.

1.	Sprue and coeliac disease		18
2.	Obstruction, band, tumour without, stone, volvulus		19
3.	Parasites: lamblia, oxyuris, ascaris, taenia, tricocephalus, ankylostoma, balantidium, bothriocephalus		20
4.	Ulcerative colitis 21 Colitis gravis 8		29
5.	Dysentery: amoebic and bacillary		29
6.	Growths, including polyposis (2)		32
7.	Loops and redundancies		45
8.	Colectomy, partial, or complete	14	55
	Colostomy, colocolostomy, ileocolostomy, ileosigmoidostomy (6)	14	
	Colopexies, including fixed caeca (8)	23	
	Gastro- or jejuno-colic fistulae	4	
9.	Adhesions of colon, largely post-operative, including caeca adherent to scars (8)		85
10.	Muco-membranous colitis, severe 13 Mucous colitis 150		163
11.	Coloptosis: Dropped colon with disorders of tone	55	202
	Coloptosis: Dropped colon with ,, ,, colitis, diverticulitis or other disease of the colon	66*	
	Coloptosis: Dropped colon with no other sign	147	
12.	Diverticulosis and diverticulitis		297
13.	Disorder of tone and segmentation: (*a*) Low tone and general inhibition	38	570
	(*b*) Irritable colon, many with prominent clinical symptoms, little or no mucus	84	
	(*c*) Excessive tone including spasm	198	
	(*d*) Other cases of general irregularity and irritability	250	
			1564

* These are also under other headings in the list and are not added into the total.

In the analysis, in various ways, of this number of cases I have been helped by my colleagues, Drs. Mary Watson, J. H. Anderson, R. S. Allison, R. Picton-Davies, and N. G. Marr, some of whom are mentioned in different sections.

Disorders classed as functional. For the purpose of this paper, ulcerative colitis is excluded; also colitis gravis, that is severe colitis, with liability to bloody stools, but showing non-ulcerative inflammation of the lining with the sigmoidoscope. Included are cases of mucous and membranous colitis in which no pure pus or pus mixed with blood was passed, and those cases of irritable colon, classified under 'disorders of tone', in which the symptoms from the colon were predominant.

The main groups of states in Table I classed as functional disorders are therefore *colonic delay or constipation, irritable colon* including nervous diarrhoea, *spastic colon and colospasm, mucous colitis* or catarrh of the colon, and *muco-membranous colitis. Coloptosis* with or without gastroptosis or general visceroptosis may be present with any of these disorders.

Most of the figures quoted in this paper refer to a *series of 242 cases* in which the colonic symptoms dominated and were, after thorough examination,

FIG. 6

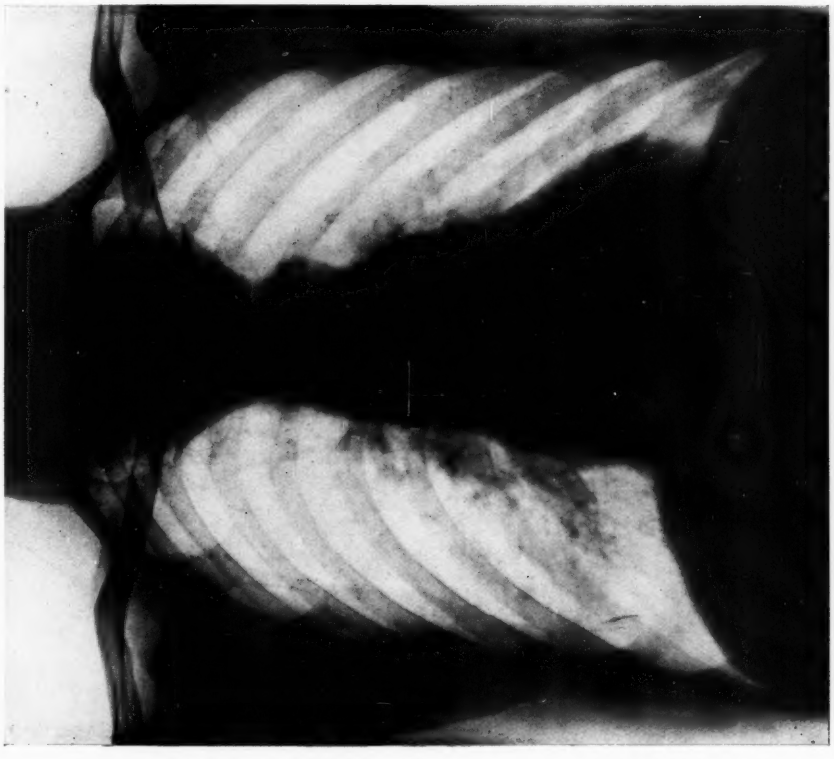


FIG. 5

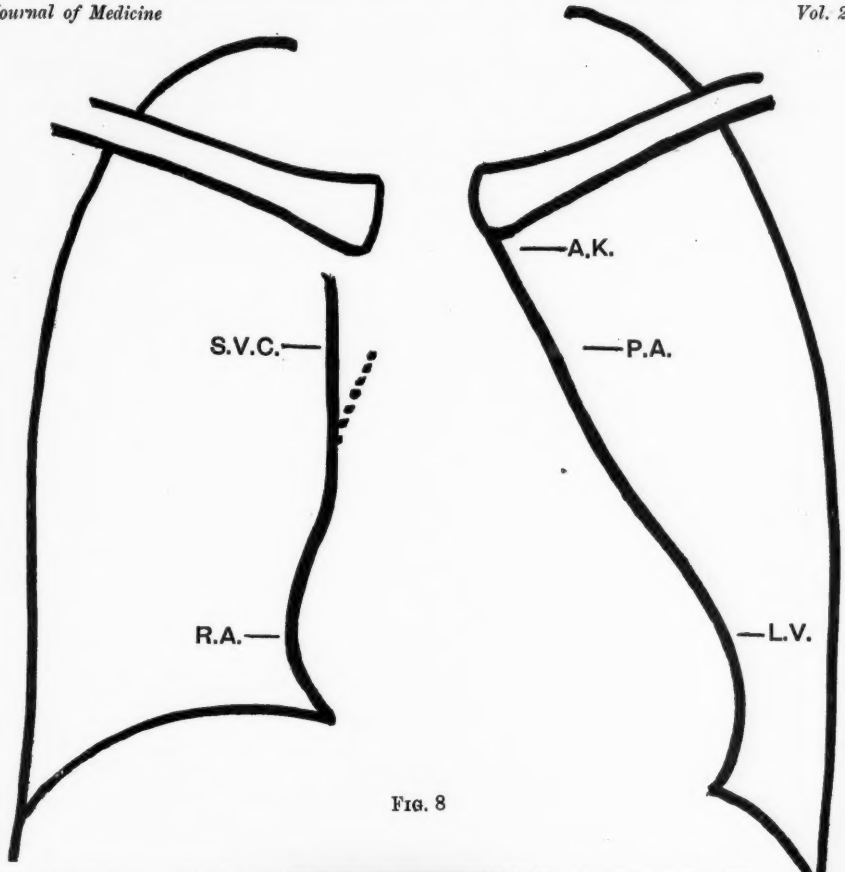


FIG. 8

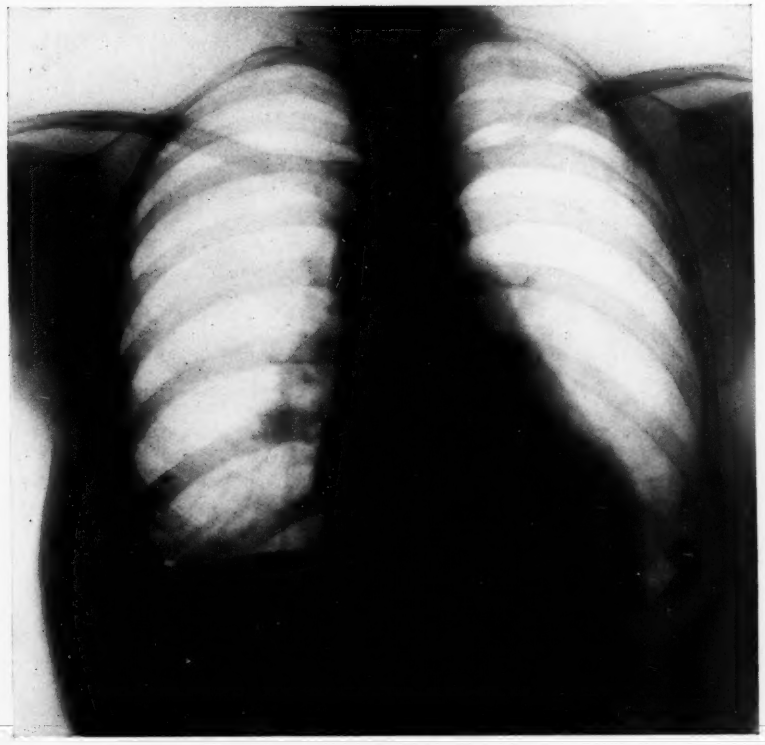
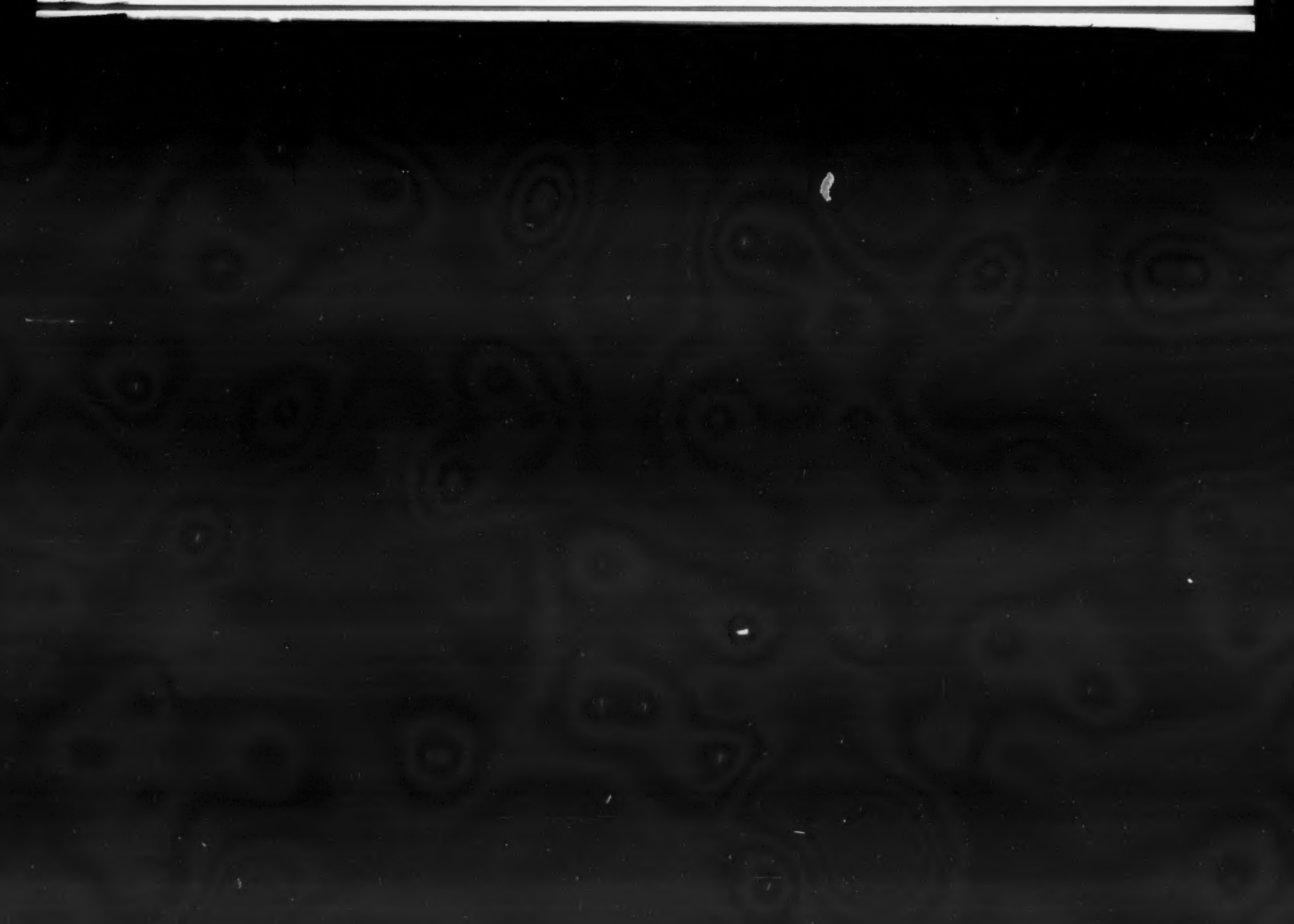


FIG. 7



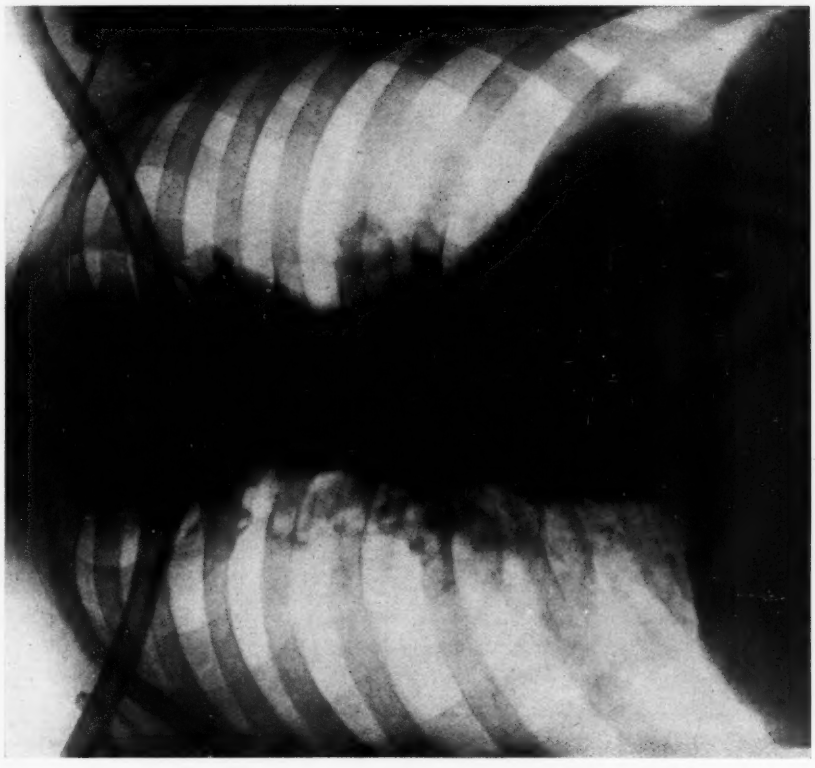


Fig. 10

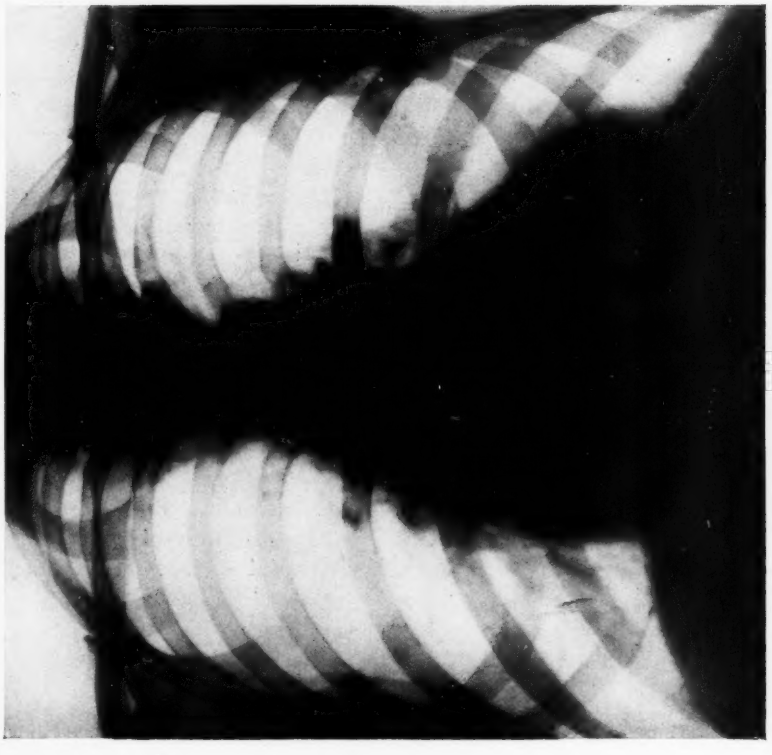


Fig. 9

believed to be the main feature. These comprise *157 cases of mucous colitis*, some of which passed membranes, and *85 cases of irritable colon, spasm and nervous diarrhoea.*

Reference is also made to an analysis (by R. Picton-Davies) of 1,000 cases of colonic delay.

The boundary between a functional disorder and organic disease of mild inflammatory type is not definite. But the distinction between organic disease and a disorder of function without any change of structure that can be recognized with the naked eye or the microscope is useful, well understood, and needs no further defence.

The term colitis, which means inflammation of the colon, should, strictly, have no place in our list. We might avoid it by calling muco-membranous colitis by the newer term of spasmomyxorrhoea. This is a sound descriptive term, though, like mucous colitis, it calls attention only to the colonic part of the disorder. But, as just mentioned, it is not certain that the older term is wrong, i.e. that there is no inflammatory change; and the bulk of our profession, to say nothing of the public, would not recognize the disease under the new name.

Before proceeding to discuss the aetiology of these conditions a brief summary may be given of the *functions of the normal colon.*

The *digestion* in the small intestine is continued in the caecum and the ascending colon. Bacteria grow here in profusion, and produce ferments which break up cellulose hulls. This process apparently begins in the small intestine (Straus). It is assisted in the large intestine by a slow passage of food, which makes up to some extent for the shortness of the human bowel as compared with that of herbivora. Thus Lorisch (quoted by McCance and Lawrence) found that 57 per cent. of the cellulose of the food disappeared from a normal intestine, but 81 per cent. from that of a case of chronic constipation. A second and main function of the large gut is the *absorption* of fluid from the chyme. To this end the area of the mucous membrane is increased by the sacculations or haustra. Thus caecal contents contain 90 per cent. of water, whilst normal faeces contain 60 to 80 per cent. In 109 estimations by my colleague, A. J. Leigh, the lowest percentage of water in non-fatty faeces was 57. In scybala as a rule it was about 70 per cent. A certain delay to allow of proper absorption is normal and may be essential. In ordinary diarrhoea fluid is, of course, lost, but as a rule little nutriment (66 b). In severe prolonged diarrhoea food value is lost as well, and this may occur when the colon is put out of action. For example, in a case of right-sided colostomy published by Monier-Williams in 1906, the patient wasted until the opening was so plugged for twelve out of the twenty-four hours as to allow the natural chyme to pass through the large bowel, when he recovered and maintained his condition. Similarly, a woman under my care became emaciated after ileosigmoidostomy, and no efforts availed to restore nutrition until the ileum was put back into the caecum, when she recovered normal weight and is still well, twelve years later. A third function

is the *secretion* of the mucus which mixes with the faeces, and renders easy the fourth function of the *passage of waste matter* along the bowel and its *extrusion* at intervals. It may be noted that most of the colon is in health not empty but full.

The movements are: (i) Pendulum or mixing movements which keep the contents moving, but not passing forwards or back. These are slow like the changes in shape of an amoeba or a cloud. They are well seen if a piece of large bowel containing opaque matter is photographed at intervals (Pl. 30, Figs. 1 and 1*a*). (ii) Transporting movements involving various partial lengths of gut and passing the contents, usually, forwards. (iii) Mass movements which may involve nearly the whole of the large gut.

Movements are dependent on the nervous plexus in the bowel wall, but are influenced by extrinsic nerves, in the proximal part of the colon mainly by the vagus, and in the distal mainly by the sympathetic. There is evidence that they are initiated from certain areas, which are likened by Keith to the nodal centres of the heart; the chief of these are described at the ileo-caecal junction, in the mid-transverse colon, and the sigmo-rectal junction. In the final act of defaecation the abdominal, pelvic, and large bowel muscles all take part.

There is a general division of function between the proximal and distal parts of the colon: the caecum, ascending and transverse colon being chiefly concerned with digestion and absorption, whilst the rest of the colon, in which lymphatics are fewer, is mainly for extrusion at intervals. The pendulum movements are accordingly greater in the proximal colon than in the descending colon, where tonic contraction is usual.

The terminal ileum contracts firmly at times (Elliot), forming an efficient valve to prevent chyme passing on or back. It is doubtful if the ileo-caecal valve can close itself when there is no muscular contraction above it; and the contents of the colon often pass into the ileum. When grateful food is taken into the stomach the terminal ileum relaxes, and chyme passes into the caecum, which then, with the ascending colon, contracts. The occurrence of this 'gastrocolic reflex' (Hurst) has been confirmed by O. A. Marxer in our X-ray room.

It appears from experimental work (Rabe) that irritation of the large intestine has no direct reflex effect on the movements and secretion of the stomach. Irritation of the small intestine, however, easily affects the stomach and vice versa. The well-known association of indigestion with disorders of the colon, such as constipation and colitis, would on Rabe's view not be due to distant working of the large intestine on the higher parts of the alimentary canal, but would depend on the condition and function of the terminal ileum and the ileo-caecal valve, and act via the small bowel.

II. *Aetiology.*

The causes of functional disorder of the colon are numerous.

Infections have in many cases at the least lowered the resistance of the bowel, the disturbance dating from an acute colitis or diarrhoea of undoubted inflammatory type. In such, and no doubt in many more chronic cases, the colon itself is the first focus. This group includes those cases of irritable colon in which the disorder is an aftermath of tropical dysentery. A group is also associated with septic infection from pyorrhoea, or other mouth or throat disorder, and with deficient chewing. The cases allied with subacidity or achlorhydria may also probably be regarded as infective. A further group is associated with disease of the gall-bladder, appendix, or other organs, including those of the pelvis, or with general chronic infections such as arthritis and fibrositis. In these last it is usual to look on the colon as the source, but this cannot always be established. In all such a continual or intermittent reinfection will go on until the source is healed.

Parasites are a cause, and among these lamblia may be mentioned. There seems to be doubt in the text-books as to how far this creature is harmful. In several cases in this series it appeared to be the cause of symptoms, which were relieved when the lambliae were absent or scarce as a result of treatment. Parasites, whether directly harmful or not, are regarded as creating lesions by which microbes profit (23).

Exposure, too much smoking, bad water, ice-water, and bad food are other causes. As regards diet it is likely that a modern 'civilized' diet is worse for the colon than a plainer one. Boas reports that in Germany mucous colitis became rare during the war when food contained less meat and more residue, with less habitual constipation. A devitamized diet also renders the gut less resistant to infection (McCarrison). The presence of a specially long colon, or one with redundant loops must be mentioned as probably conducing to delay.

The two main causes, according to nearly all observers, are *neurosis* and *constipation.* Many observers hold that the cause is constipation and that neurosis results.

My experience leads to the view that an unstable nervous system, inherited or acquired, is a predisposing state (4). A family history of cancer, tuberculosis, or nervous disturbance was given in 39 per cent. of these cases. We see the spoilt and introspective type of neurosis, and the unselfish never resting type. The pronounced form of functional disorder known as enterospasm is usually found in those engaged in mental work.

Nearly every one is agreed that the immediate exciting cause of functional disorder of the colon is constipation. Of the almost constant complaint of former or present constipation there can be no doubt. But I venture to put forward the view that the treatment for real or alleged constipation, namely, that by irritating aperients, is as potent and frequent a cause of colonic disorder as

constipation itself. The abuse of aperients is, of course, recognized by many writers on this subject as a cause, with other chemical irritants, of non-infective colitis; but it is generally held that constipation or intestinal stasis is the primary evil. This is no doubt true in many instances, but as a general rule it is not established; and the fact that so many people with colonic disorder who complain of constipation are regular aperient takers is impressive.

Thus of 242 cases of functional disorder there were 47 with diarrhoea who took no aperient. Of the remainder there were 18 only of whom it is recorded that no aperient was taken. Of 50 others, the history in this respect is uncertain; all the rest stated that they took aperients of some kind, 70 of them, or half, taking a purge every day.

Picton-Davies, in a recent analysis, has found that out of 1,000 patients in this hospital, in whom abnormal delay in the bowel was present as shown by the barium meal, 764 complained of constipation. Of these 670, i.e. six out of seven, were taking aperients, and no less than 431 doing so every day. Such as these, who really had constipation, do not, however, comprise all the aperient-takers, for we see many who complain of constipation and take purges themselves on that account in whom it is found that there is no delay in the passage of the barium meal. Further, delay is often found in those who have no prominent symptoms referable to the colon. In the above series, for example, there were 236 people who were unaware that the bowel was passing on its contents at a slower rate than normal, and were naturally taking no aperients. The number of colitics among them, twelve, or 5·1 per cent., is less than half the proportion found among the remainder.

My impression is, therefore, that moderate constipation is less harmful to the colon than the treatment of it by irritative aperients. These interfere with the rhythm of the bowel, setting up inhibitions and spasms, causing first a too rapid passage and later local stases; they render the faeces more fluid than they should be and thus favour abnormal bacterial and putrefactive growth. Among irritative aperients, besides calomel and the drastic vegetable purgatives, are included the vegetable laxatives, such as rhubarb, cascara, and senna, which contain a chemical irritant, one of the anthracene bodies. I include also the regular use of salines. The action of these is osmotic rather than irritant, but they interfere with the normal time relations of the passage of material through the bowel, and lead to the discharge of much more of the colon contents than in a normal action.

Fruit preparations are not classed as irritants, nor are substances which act by swelling, such as agar and psyllium seeds, or simple lubricants such as pure paraffin. There is nothing in the history of these cases to show that the use of such aids has a relation to colonic disorder.

The ease with which aperients will bring on an intractable colitis in constitutional disease, such as Bright's disease, is well known.

Age. Functional disorders of the colon are most prevalent in young middle age. The average age of 242 cases was 44 years for men and 42 for women. As regards membranous colitis, Hale-White found that it began between 20

and 40; also that five women were affected to one man. Dawson thought that the proportion of males, which he gave as 25–30 per cent. was increasing. In this series, which includes cases of mucous colitis and of irritable colon, the proportion of males is greater—96 men and 146 women, i.e. more than half.

The following table summarizes the main points of the *family history* in the series.

TABLE II.

		No. of cases.	Percentage in 242 cases.
Cancer		43	18
Tuberculosis		29	12
Neurosis	Neurasthenia	10	9
	Migraine	6	
	Asthma	3	
	Epilepsy	2	
			39

Such figures usually understate the case. The family association with the above diseases shows that many of the patients, probably more than half, inherit constitutional weakness.

Example. Case of familial influence and nervous predisposition. *Mucous colitis* with alternating constipation and diarrhoea.

3788. Married. A woman of 33 whose three brothers were consumptive had been subject in childhood to diarrhoea and flatulence after emotion. She had suffered for ten years from diarrhoea following bouts of constipation, or at the period, passage of mucus, rumblings, nervousness, and loss of sleep and weight. There was tenderness along the course of the colon. With X-rays an ileal coil was adherent to an appendicectomy scar, there was spasm of the ascending, and delay in the descending, colon and the rectum. With rest, diet, encouragement, poultices, paraffin, and a vaccine the symptoms disappeared and half a stone was put on. She kept well on regime, diet, and rests, but returned eighteen months later with a *B. coli* cystitis which yielded to treatment. The original symptoms remained absent.

Occupation. The mental effect of colonic disorder is great, but, conversely, colonic function is powerfully influenced by the mind. My co-worker, J. H. Anderson, remarks that in Gallipoli, which he describes as the greatest mass experiment of bowel disorder of which there is record, it was found that sick parades, which were mainly of dysenterics, fell almost to nothing before heavy fighting. If courage and duty could temporarily influence a true infective colitis, the same applies *a fortiori* to the cases here discussed. The lack of occupation of many of these patients is obvious. Work would cure some and prevent the illness of many.

III. *Pathology.*

Whether the nervous factor is the primary one or not, there is a local neuromuscular disturbance, which in certain cases may be reflex from associated disorders (see p. 549), but in others is due to irritation from the mucous membrane itself. The irritation may be bacterial at first, as is seen when

disorder follows specific colitic infections; it may also be toxic. The mucous membrane is resistant to bacteria and toxins as many experiments have shown, from which it is concluded that a general infection from microbes or the absorption of poisons does not as a rule occur unless the lining of the bowel is damaged. It may, however, be damaged by a variety of causes. Ulceration comes first, but is not within the range of discussion here. The great resistive powers of the mucous membrane are sometimes overcome however, without, or before, ulceration, in certain infections, in which the germ arrives by way of the alimentary canal, e.g. in typhoid fever. In devitaminized animals also the mucous membrane is invaded by germs; and in radiation experiments coliform organisms and agglutinins have been found in the blood.

I should like to suggest another way in which the vitality of the bowel is likely to be lowered. One of the forces which moves on the venous blood in any piece of bowel is the continual contraction and relaxation of the muscle. If the bowel is sluggish venous blood is likely to remain longer in it and the mucous membrane will be less well nourished and more vulnerable. Further, this may be why flatulence is apt to occur when there is undue stasis in a loop of gut. The blood soon becomes saturated with whatever gas there is in the bowel and can take up no more, or perhaps may even give off gas to the lumen. It is known that when circulation is arrested in any loop, as with thrombosis or volvulus, it distends, and it is reasonable to suppose that with the partial circulatory arrest of venous stasis the same may occur in less degree. Indeed, flatulence in general is more often connected with a disturbed motility of the bowel than with the 'fermentation' or decomposing of delayed matter to which it is ascribed. In the cases of functional disorder, such as we are discussing, this circulatory factor may be of importance.

It is believed that microbes do pass in small numbers into the circulation and tissues, and are constantly destroyed by the various protective mechanisms, of which the liver comes first. If the liver is unable to destroy them they may damage it and other organs. The same applies to any absorbed toxin.

There are, therefore, three lines of defence against poisoning from the intestine—first, the mucous lining of the gut, secondly, the liver, and thirdly, the tissues generally. As regards the formation of toxins the intestinal bacteria can and do make poisons, e.g., from excessive protein cleavage, but we know that this 'permanent menace is met in health' (1), and we do not know how great a part it plays in disease. In a few conditions the evidence seems clear, as when rashes arise after certain foods, or in the poisoning from ptomaines; and in the severer types of colonic disorder the association of ill health, headaches, poor circulation, lassitude, and neurosis leads naturally to the view that one or more of these lines of defence has yielded.

But the theory of intestinal auto-intoxication has been pressed rather far. In milder conditions the relief which many feel after a good action is too rapid to be explained by the disappearance of a toxin, and, as Hutchison remarks, there is no proof that the absorption of poisons from the intestines produces many

of the symptoms attributed to it. Indeed, in constipation without secondary irritation the number of bacteria is less than usual; and there is more toxaemia from loose than from constipated motions. Scientific bacteriologists tell us that much of the alleged evidence of abnormal growths in the faeces does not survive examination, and Ledingham remarks that there are probably more names than bacteria to correspond (39, 13).

There is danger in a too facile diagnosis of intestinal auto-intoxication, for our experience is that a good proportion of the patients sent to hospital so labelled prove to be the subjects of some organic lesion (66 a). For example, in ninety cases admitted with that diagnosis, thirty-two were found to be suffering from the following diseases—gastric or duodenal ulcer (8), diverticulitis (7), cholecystitis (6), syphilis (3), growth of the rectum (2), growth of the lung, nephritis, gout or heart disease; and in the remainder the main feature is often neurasthenia.

In the pathology of muco-membranous colitis, the nervous factor is so prominent that few can regard it as secondary. Some allergic influence is nowadays suggested, on the analogy with asthma, urticaria, and angioneurotic oedema (31, 75).

Morbid anatomy. In functional disorders of the colon there is little or no change to be detected in the bowel. If there is inflammation it is evidently of low grade. The lining is often found normal with the sigmoidoscope; in severe mucous colitis it may appear rather more brick red than usual, or in long-standing cases a little greyer. Spasm of the sigmoid is sometimes firm, with corrugation which resists, but ultimately yields to, inflation. But often the shreds of mucus are the only visible sign. These may also be caused by a preparatory enema, a fallacy to be borne in mind. Muco-purulent discharge is a sign of an added infection, whilst yellow pus or blood point to inflammation or other lesion. Ordinary faecal mucus does not contain pus, though a few leucocytes may be seen. In the milder forms of chronic colitis Keith reported some pigmentation, and dilatation of lymph vessels; also changes in the nerve plexus of Meissner and Auerbach similar to those he had found in devitaminized animals. Prolonged intestinal stasis may set up a low form of peritonitis with free formation of adhesions, but generally does not; there may be great delay without any such complication. In severe muco-membranous colitis Hale-White found *post mortem* a thin atrophied colon, with here and there one or two patches of congestion.

The membranous shreds and casts consist of a structureless mucin with epithelial cells, debris, and phosphatic crystals embedded therein. Sometimes they contain a few red or white corpuscles, especially eosinophils, intestinal epithelial cells or Charcot-Leyden crystals. The marks of folds of the mucous membrane and of follicles may be seen on the casts, as described by Wilks in 1859.

Bacteriology. The micro-organisms usually found are of the coliform, streptococcal, and anaerobic groups, of which subvarieties are described, based

on the chemical effect of the culture on various media; it must be remembered that other varieties may be equally active in the intestine, and that unless special cultures are made anaerobes are often not reported.

In the coliform group it is theoretically possible to detect by agglutinin tests to what bacterium the blood has reacted (18), though the practical value of the method in mucous colitis is not established.

It is usual to attempt to estimate the proportion of streptococci in the motions by counting colonies, and to test the haemolytic power. It has been thought that because an organism is haemolytic it is parasitic: but feebly haemolytic streptococci in the faeces are common and not necessarily of importance. The more frequently and carefully streptococci are searched for the more often they tend to be found. Neither are agglutination tests usually valuable in this group. Indeed, the justification, if any, for the enormous use of faecal streptococcal vaccines must rest upon clinical experience, for scientific proof is so far wanting. Cruickshank remarks, 'only those who have a very restricted view of the flora of the intestinal contents, and a very limited knowledge of the wide variations which occur in health, can with confidence recognize an "abnormal flora" and prescribe accordingly . . . Whatever may be the therapeutic results obtained with vaccines, it is not justifiable to associate these common inhabitants of the intestinal tract as standing in causal relationship to the patient's pathological condition.' In the severer forms of infective colitis we are on surer ground, and various organisms are detected as the cause, including the dysentery and pseudodysentery bacilli in true dysentery: and in the 'food-poisoning' group *paratyphosus B* from human sources, *B. enteritidis* from cattle, and *B. aertrycke* (*suipestifer*) from cattle and pigs.

My colleague, J. G. S. Jeffery, working with S. W. Patterson, has made a practice of culturing all motions in the routine examination of faeces. Cocci were found in 68 per cent. in 2,000 faecal cultures of all kinds, plated upon blood agar.

The following table shows the frequency of cocci and atypical *B. coli* obtained in recent cases: (i) in motions of varying consistency; (ii) in those of colic delay, proved radiologically, and compared with those of a normal rate of passage and with diarrhoea; (iii) in mucous motions.

TABLE III.

	No. of Cases.	% of Cases. *Streptococci.*				Atypical. *B. coli.*
		None.	Few.	Abundant.	Total.	Slow Lactose Fermenters.
	1	2	3	4	5	6
Scybala	63	46	32	22	54	8
Colic delay	80	36	36	28	64	9
Normal rate	46	35	24	41	65	11
Diarrhoea	17	24	52	24	76	12
Mucus	87	31	32	37	69	12

In making this table motions which were not fairly fresh on reaching the

laboratory were excluded; also those known to be the result of aperients, and (except in the cases of clinical diarrhoea) all very loose and oily motions.

The figures in column 5 seem to indicate that streptococci tend to be less common in constipated and more common in loose motions, but the differences are too small to stress. The growths obtained from mucous did not differ greatly from those of non-mucous motions. When mucus and faecal matter were cultured from the same motion the results agreed as a rule. The mucus gives a luxuriant growth, but the faecal matter tends to yield the more cocci.

It may be concluded that it is important to examine and culture the faeces in order to exclude pus, blood, parasites, and known pathogenic bacteria, i.e. in order to make a diagnosis. It appears, however, that in the present state of our knowledge the repeated culture of the motions in these disorders is probably not worth the time and labour involved.

IV. *Symptoms and Signs.*

In functional disorder of the colon the disturbance may vary from little or none in many cases of simple constipation to complete invalidism with much suffering in severe mucous colitis.

As regards constipation, reference may be made to the symptoms noted in the study of a series of 1,000 cases of radiological colonic delay (Picton-Davies). This included patients with a variety of disorders, but the figures have nevertheless a bearing on our subject. It is mentioned above that 764 were aware of constipation; and that of these aperients were being taken by 670, and by 431 daily. Five hundred and twenty-one complained of discomfort or pain in the abdomen, and the same number of flatulence, 289 of headache, 181 were depressed or neurasthenic, 159 had piles, 182 a furred tongue, i.e. 18 per cent., 12 per cent. pyorrhoea, and 9 per cent. anaemia. A muddy complexion was noted in 44, i.e. 4·4 per cent. Most of these 44 patients showed considerable delay in the whole colon; in 5 the delay was in the rectum only, and it was not severe.

In 98 of these 1,000 patients a diagnosis of colonic disorder, other than delay, was made, i.e. in 10 per cent. Of these, 11 had diarrhoea. Of the remainder, 75 were in the group of those who complained of constipation, 65, i.e. the great majority, of whom were aperient takers.

The summary in Table IV, on the following page, refers to 242 cases of colonic disorder.

Discussion of Table.

Alimentary symptoms. Some kind of pain or discomfort was complained of by 80 per cent. of the patients, ranging from an ache or dragging, or colicky pains, cramps, distension with gurgling, and flatulence, and various curious sensations to acute paroxysmal crisis with vomiting. Pain with tenderness is usually over the colon (55 per cent.), but may be epigastric (26 per cent.); and

as it often occurs soon after food, as in other nervous dyspepsias, it may not be possible from the situation to say whether it arose in the stomach or transverse colon. Jordan and Kiefer in their analysis of 200 cases found epigastric distress to be commoner than the generalized, and least common that in the right lower quadrant. Our series agrees with this except that pain in the left lower quadrant was as frequent as in the right. Pain and tenderness are usually intermittent (28 per cent.) with intervals of complete or comparative comfort; in the severe cases, which are uncommon (8 per cent.) it may be continuous. In a typical membranous colitis an attack may begin with nausea and vomiting, succeeded by severe pain along the colon, during which the patient may be aware from which part of the gut membrane is separating by a raw, painful feeling, relieved at length by extrusion of a cast.

TABLE IV.

Diagnosis.

Mucous and non-membranous colitis	157
Irritable and spastic colon	85

Symptoms.

Pain: 123; discomfort 69; dragging 28; colicky 25; cramps 11; griping 8; epigastrium 49; at or below navel 40; right iliac fossa 33; left iliac fossa 32; intermittent and variable 68; after food 22; continuous 15; after motions 13.

Flatulence: 131; distension 46; gurgling 11.

Appetite: none 4; poor or capricious 57; normal 20.

Nausea: 59; vomiting 38.

Bowels: constipation 99; irregular, or alternate constipation and diarrhoea 53; diarrhoea 47; regular daily 23.

Neurosis: 48; depression 40; insomnia 21; mental 2; headache 63; backache 26; giddiness 16.

Weariness: 100; palpitation 43; dyspnoea 22; anaemia 26; cold hands and feet 23; shivering 5; malaise 9; fever 4; asthma and hay fever 3.

Signs.

Nutrition: normal or fair 115; poor 75; obese 21.

Tongue: clean 125; dirty 82; white 3.

Teeth: good 117; indifferent or diseased 50.

Abdomen: tender 77; distended 31.

Gastric juice: (111 cases) superacid 46; normal 38; subacid 25; no free acid 2.

Faeces: mucus with or without shreds 131; loose 71.

X-rays: Delay—general 73; irregular contractions with local hypertony and spasm 123; inhibitions at various parts, usually in the distal colon, and with the enema 76; rapid passage 9.

Blood-pressure: average 128/77.

A prominent symptom is a poor appetite, even anorexia in severe cases. Nausea is common (24 per cent.), and vomiting not infrequent (16 per cent.). There may be food phobias. The tongue is often clean: it was so in half these cases; in a third of them it was dirty or white. It tends to be flabby and marked with the teeth.

Constipation is almost universal in these disorders. If diarrhoea is mentioned it is (except in the small group of nervous diarrhoeas) often due to a

secondary irritation and infection from constipation, and is intermittent. Thus although forty-seven patients complained of being subject to diarrhoea, in nine only did X-rays show a rapid passage through the bowel. It is usual to find that strong aperients have been used for years.

A post-dysenteric variety of diarrhoea is an aftermath of the infection; it is at first inflammatory, but a neuromuscular irritability may remain a long time, and when it has subsided under treatment may be aroused again by slight causes.

A true nervous diarrhoea is less common. In such cases there is often a motion on rising and a tendency to a further one after any meal. This is more liable to happen on special occasions, so that the subject fears to take part in a function, or even to take a meal away from home, or go to the theatre. The patients are often able people with anxious occupations. There is an exaggeration of the natural discharge of the ileal contents into the caecum after food and of the extrusive reflexes, ceasing when the bowel is emptied. On macro- and microscopical examination of the stools nothing pathological is found except excess of water. The rate of passage, as seen with X-rays, is not always as rapid as would be expected and may be, in these patients also, slower than normal.

The chief nervous symptoms in functional colonic disorders are weariness, depression, and headache. Vitality is low and mental energy capricious or absent. Duties are carried out at the price of great effort and followed by exhaustion. Lord Dawson has rightly remarked that some of these folk who bear up bravely against their illness are not neurotic but heroic. Others give way and fall into intestinal neurasthenia with delusions of interpretation of symptoms. In these, experience teaches that, when possible, all motions should be saved for inspection, since the patient's report of their number, bulk, and nature may be far from the truth. On the one hand, the account of the mucus may be exaggerated, and on the other he may be unaware of the presence of mixed mucus. Headache, often occipital, and backache are common.

Of general symptoms malaise is frequent and associated sometimes with a rise of temperature of a degree or so in the week before a menstrual period; and at a time of mucous or membranous discharges, when there may, in the rarer severe cases, be a rigor. In such anaemia is usual, sometimes with a muddy complexion, and emaciation, palpitation, giddiness, dyspnoea, heart pains, and cold hands and feet.

In the group of cases of irritable colon the chronic nervous symptoms may be present as in muco-membranous colitis, but are less severe and less paroxysmal.

In colospasm the symptoms are paroxysmal, but without the mucous discharges. This complaint occurs in the mentally active, and especially at times of overwork and emotional stress. Attacks are ushered in by various acute symptoms such as rapid pulse, oppression, shivering, vertigo, and numbness, and may be severe and alarming.

Signs.

The abdomen often appears normal on inspection: distension was noted in 13 per cent. of these cases. Retraction is not more than is explained by the thinness of the patient. In spastic cases the bowel can often be felt, but experience is needed to be sure that this is abnormal: it is often palpable in the left lower quadrant in patients without symptoms. It is abnormal to feel the ascending or transverse colon as a hard cord.

The gastric juice is not weak so often as has been thought. In this series there was achlorhydria in 2 per cent. only of the 111 cases examined in this respect, and subacidity in 23 per cent. 41 per cent. were superacid.

The faeces may be characteristic of the different types of disease. A little mucus with a constipated motion is not to be looked upon as abnormal, nor is some mucus mixed with the faeces. In the type of irritable colon with constipation there are scybala or fragments with some mucus around them. In catarrhal colitis the mucus is increased, and in a chronic case the typical motions are not hard but semi-solid mixed with an excess of mucus derived from the upper colon. This the patient often describes as diarrhoea. In membranous colitis large casts may appear, apart from faecal matter, as rolled-up membrane, the nature and extent of which is not recognized until it is floated out in water. There may be bleeding before or after the passage of membrane. Long and narrow stools are sometimes passed and complained of, and are in the absence of organic lesion to be ascribed to spasm of the sphincter. They indicate the reflex nervous state rather than local disorder.

Intestinal sand was found by Hale-White in less than 10 per cent. of the cases of membranous colitis. It occurs intermittently and as much as a tablespoonful may be passed in a day. It is mostly calcium phosphate, with traces of oxalate, magnesium, iron, and perhaps silica. It is suggested that lack of bile is a cause of intestinal sand; but it is not observed, so far as I know, when that secretion is absent from the gut.

Radiology. The standards of normal radiology for the colon arrived at in this hospital are briefly set forth as follows.

The rate at which the parts of the normal colon are filled with, and pass on, an opaque meal varies with its nature. Mr. O. A. Marxer, by whom the X-ray work referred to in this paper has been done, uses a meal of barium sulphate suspended either in buttermilk or malted milk. This is slower in passage in the stomach and colon than a carbohydrate suspension, but shows more detail, except in the small gut. The caecum begins to fill on the average four hours after the meal and the small intestine should discharge all its contents therein four-and-a-half hours after the stomach is empty. At five to six hours the hepatic flexure or midcolon, and at nine to twelve hours the iliac colon is reached. At twenty-four hours, before defaecation, there should be a coating only in the ascending colon, the material lying from the hepatic

flexure to the rectum. At forty-eight hours, before defaecation, the remainder of the meal, about half, lies in the distal colon. All should be evacuated in from forty-eight to seventy-two hours, except that a coating may remain in the distal colon until the next action.

When a barium meal is passed on from any part of the colon that viscus does not remain empty, the opaque meal being followed by the residues from later ordinary meals. The tonically contracted descending colon, however, may hold very little. The rectum after defaecation should be empty.

The haustra in health are symmetrical, with a smooth scalloped outline. The nodes or constrictions between them and the total diameter of the bowel vary according to the degree of tone.

When the transverse colon is full it may descend at its middle to the brim of the pelvis or further, the subject being erect (Pl. 30, Fig. 2). This is not abnormal, for twelve to twenty-four hours later the same piece of bowel may be seen (Pl. 30, Fig. 3), in a different state of tone, to lie across the abdomen with only a slight bow from the hepatic to the splenic flexure. Just to the left of the spine the lumen of the transverse colon is generally seen to become narrower.

When a mass movement occurs the bowel loses its segmentation and contraction sweeps onward, the contents moving rapidly into the piece of bowel lying in front, which can be seen to dilate to receive them. Such mass movements (Pl. 31, Fig. 4) occur mainly after a meal or evacuation: they begin normally in the proximal transverse colon.

The caecum may lie in the pelvis, but with manipulation, breathing, and change of position, can in over 90 per cent. of such cases be brought into the iliac fossa.

We find the capacity of the normal colon to be in the morning about 30 oz. when fluid is run in under low pressure. After defaecation it is less. The average length of the ascending colon and caecum when filled is 25 cm., of the iliac colon and sigmoid up to 40 cm., of the whole colon 125–175 cm. The diameter of the transverse colon of normal tone is 4 to 6 cm., of the descending colon and sigmoid 3 to 4 cm.

A barium enema should be of a standard suitable bulk. If too large the bowel may be distended and elongated, even to simulation of redundancy. Pl. 32, Fig. 5, shows the same bowel filled with the standard amount of 40 oz. (1,100 c.c.) and Pl. 32, Fig. 6, the lower picture, with twice that amount.

Radiology of the functional disorders of the colon. The rate of passage along the bowl may be quicker or slower than the normal laid down above, but is nearly always slower, even when the motions are semi-solid, and the patient complains of frequency.

If barium lay in the ascending colon, after defaecation, at more than twenty-four hours, we should call that slight delay. The term great delay would be used with this meal if there were, after stool, an opaque residue in the ascending or transverse colon at forty-eight hours, or in the distal half of the colon at seventy-two hours.

The situation of the main delay in the above-mentioned series of 1,000 cases (R. Picton-Davies) was as follows:

TABLE V.

	Per cent.
Whole colon	53·0
Caecum	0·9
Ascending colon	0·7
,, ,, and transverse colon	1·3
Transverse colon	5·1
,, ,, and sigmoid	4·0
,, ,, ,, rectum	1·0
Descending colon	1·8
,, ,, and sigmoid	2·2
Sigmoid	11·2
,, and rectum	6·7
Rectum	11·2
	99·1

It appears, therefore, that delay was in the whole colon in half the cases. Caecal delay was rare: it may probably be nearly always regarded as evidence of a local inflammation. Pure rectal delay was found in 11 per cent., whilst sigmoid and rectal delay together accounted for nearly a third of the cases.

Apart from the rate of passage, other early radiological signs of disorder of function of the colon are those of an increase or lessening of the tone of the muscle. Such was observed in 43 per cent. of the 242 cases of colonic derangement (Pl. 33, Fig. 7). The sluggish (hypotonic) bowel has a wider lumen and is, I believe, also longer. The haustrations are open, there is less change from time to time, and delay results. It is commonest in the transverse colon and the sigmoid, but may occur all along the bowel, as we found in one-third of this series. These are cases of hypotonic, sometimes called atonic, constipation. Complete lack of haustration is a more acute sign, due to active nervous inhibition. It is seen in severe colitis (Pl. 34, Fig. 12) with the barium meal; and in mild colitis and some other cases as a result of the injection of a barium enema.

In the hypertonic bowel the whole lumen is reduced, the nodes or constrictions being deeper and the total diameter shorter.

The irritable, or better, the irritated bowel shows irregular contraction of the muscle (Pl. 33, Fig. 8). Such interference with normal haustration is a common early sign in functional derangement of the colon, the faeces being divided into separate pieces of varying size, often with delay. It was observed in 29 per cent. of the series.

If a whole segment of bowel remains contracted, the contents being squeezed out so that the column of material is deformed or interrupted, that is spasm (Pl. 33, Fig. 9). This is commonest in the distal part of the colon, next in the transverse colon. It is less often seen in the caecum, unless there is local disease.

Apart from general sluggishness of the bowel the disorder of the colon is generally a mixed one, hypertony or spasms and inhibition being present at various parts. The importance for treatment of recognizing the nature of the delay is clear. All stages of irritation and failing function can be recognized in different patients.

Antiperistalsis is observed in the colon in rare cases of severe constipation; but seems to be associated with an abnormal irritation. For example, one patient in whom the contents of the tranverse colon moved to and fro to the caecum had had dysentery. The backward movement of contents is often seen after the introduction of a barium enema.

V. *Associated Diseases and Disorders.*

The presence of some functional disorder of the colon is common when there is organic disease in the abdomen. Cases in which the colonic symptoms, if present, are obscured by, or are clearly secondary or subordinate to, another disease are not included in this series. But even if attention is confined to cases in which the colonic symptoms are the predominant feature, there is still a large proportion in which there is, or has been, some lesion near by. In these 242 cases in which after a full examination the diagnosis was mucous colitis or irritable colon, and to which, as will be seen, treatment for the colon was applied with success, in 123 (50 per cent.) there was, or had been, present, or suspected, some other disorder of the alimentary system, the main ones being appendical irritation or inflammation, gall-bladder disease, ulcer of stomach or duodenum, adhesions, parasites, and duodenal pouches. Many of these patients would be envisaged wrongly if the symptoms, signs, and faeces only were studied, and no further examinations made.

The appendix was diseased or suspected in fifty-nine, or 24 per cent., and in a large number had been removed. The appendix is part of the colon, and the catarrhs and derangements of either may spread to the other. When diseased, the appendix carries the greater risks, and if after careful investigation there is evidence, clinical and radiological (and 80 per cent. of appendices can be seen with a good barium technique), that it is diseased, it is wise to have it removed as a first step in treating the colon. But it is often taken out in vain. The diagnosis of appendicitis and the removal of that organ are easy and dramatic steps which appeal to the public more than do the quiet inquiry, observation, and prolonged treatment called for by colonic disorders. Hence the common rule is, operate first and investigate after. The practice as applied in this and other non-acute abdominal conditions is not a credit to our art. It is now more than thirty years since Treves pointed out that the chief reason for the failure of appendicectomy to relieve symptoms was the presence of colitis.

W. Goldie has called attention to the prevalence of mucous excretion in disease of the gall-bladder and has brought forward an interesting group of cases. In our series cholecystitis or cholelithiasis was recognized in twelve out of 150 cases of mucous colitis.

As an example of a reflex mucous colitis from another cause, a stone in the kidney, the following case may be quoted.

A man of 36 complained of pain in the left loin and back, flatulence, retching, constipation, the passage of pieces of mucus up to nine inches long, and

nervous exhaustion. He had been unwell on and off for eleven years; severe pains began two-and-a-half years ago. He had been formerly X-rayed and treated for mucous colitis. On examination a stone was detected in the left kidney. The transverse and descending colon showed spasm and irregular haustration. After removal of the stone neither the symptoms nor the mucus recurred. Ten years later he was still well.

In colonic disorder, as in other functional states, such as headache, there are often three factors: (1) The predisposing state, a lowered muscular and secretory power, i.e. poor health or deficient vitality. (2) Some outside adverse factor, such as those lesions now being discussed, or septic teeth. (3) An immediate exciting cause of dysfunction, such as, in the colon, the irritation of constant aperients or hard faeces. No. 1 we can influence little, or only very slowly, but factors 2 and 3 can often be dealt with; and removal of either of them may do much good.

The combination of functional disorder of the colon with visceroptosis is well recognized. We regard the colon as dropped if the transverse part is low and the hepatic flexure in the iliac fossa, with or without dropping of the splenic flexure below the left iliac crest. The summits of the bends must be seen, as they may be filled with gas. In this series a dropped colon is recorded twenty-nine times, i.e. in 12 per cent.

The colon is often dropped without being the seat of recognizable symptoms. My experience agrees with that of Barker who says that in a small number of cases only, and these extreme, are symptoms caused by the ptosis.

As regards the association of ptosis and delay, O. A. Marxer, some years ago, in 200 cases with about an equal proportion of colons of high, normal, and low position, found the average rate of passage approximately the same in the three groups. There was a 15 per cent. excess of delay in women as compared with men, irrespective of the situation of the bowel. Recently Picton-Davies found that out of 141 cases of dropped colon, in thirty-eight, 27 per cent., there was great delay, i.e. for ninety-six hours or more after the meal; in fifty-five there was no delay and in thirty-five others it was moderate only, i.e. between sixty and seventy-two hours' passage. Hence in more than half the retardation was inconsiderable. In view of these figures it appears that the thesis that dropping of the colon is *per se* a cause of a slow passage of its content is not established.

The colon is made to be a mobile organ and it does not matter much where it lies so long as its walls are healthy, and mix and pass on the contents without abnormal haste or delay. It is probable that delay is far more often due to a deficient or disordered muscular power, that is, to loss of function, than to the mechanical results of its situation. That the immediate cause of stasis lies in the bowel wall, that it is the muscle and the innervation that count, and that anatomical irregularities are seldom important, was put forth strongly by Dawson in 1921 and is borne out by these observations. It is also confirmed by the fact that, although in some the position of the viscera improves with treatment, others may get well with little or no alteration thereof (66 a).

In so far as severe ptosis favours delay it leads to irritation, oversecretion of mucus, hyper- and hypotony and spasm. The resulting pain and loss of sleep lower the tone of the abdominal muscles and the nervous system generally, leading, with the pull of the loaded colon, when erect, to more ptosis, spasm, and delay. Stress is rightly laid by writers upon this vicious circle. The argument does not, however, apply to every case of ptosis. The dropping, like the delay, is probably as a rule the result of poor general tone. This view is also supported by the change in the state of the bowel and the loss of symptoms after steady treatment, as described below; and these results correspond with those recently reported by Jordan and Kiefer.

Poor tone generally involves the muscle and the nervous control of the wall of the abdomen as well as of the gut; but not always, for the writer has seen extreme ptosis of the stomach and bowels with good abdominal muscles.

Redundant loops. A long or large sigmoid loop or an extra loop of the transverse or descending colon is often observed, and especially in cases of constipation (Pl. 34, Fig. 13). It was noted as regards the sigmoid thirty times in 1,000, but this is an under-statement, for earlier cases were not always recorded. Kantor observed it in 19 per cent. of 1,000 patients. In such patients more fluid than the normal 40 oz. may be needed to demonstrate the whole bowel by means of a barium enema.

It is often assumed that a redundant colon is congenital and that it predisposes to constipation. The fact that the length of the large bowel varies a good deal at birth lends support to the view 'that many people are born with a large intestine too long for comfortable disposition in the abdominal cavity, necessitating its arrangement in exaggerated or adventitious loops, which might properly be termed redundant' (65). No doubt this is sometimes so, but for many years my impression has been that much of the redundancy seen is acquired, though I have not been successful in obtaining good evidence, since our earliest accurate X-ray records do not yet go back twenty years. If the muscle of the bowel is as a rule abnormally relaxed the gut will be longer as well as wider; and continued sluggishness might then be expected to lead to the gradual development of a state which is on the way to what we see in chronic obstruction; and I suggest that many 'long colons' are the result of decades of constipation. Fitzwilliams, in 1911, described a case indistinguishable from what is called congenital dilatation of the colon, without obstruction *post mortem*. At removal of the appendix some years before no such dilatation had been seen.

VI. *Diagnosis.*

The diagnosis of functional disorder of the colon calls for much care; for the risk of labelling a disease as functional which is due to an organic lesion is considerable. It is least in a definite case of muco-membranous colitis, but is still present.

The diseases most likely to be confused may be classed as follows:

1. Those causing dyspepsia, such as gastritis, gastric and duodenal ulcer, gall-stones, and appendicitis. The error here is usually to suspect the presence of one of these complaints when the discomfort after food or other dyspeptic symptom is due to colitis.

2. When the prominent symptoms are referable to the colon we must exclude the dysenteries, colitis from parasites, diverticulosis and diverticulitis, and chronic obstruction from organic causes, especially cancer.

3. Diseases arising from without the colon, which may cause symptoms simulating functional colonic disorder are: achylic and pancreatic diarrhoea, appendicitis, Graves' disease, diseases of the ovaries, tubes, or womb, not forgetting prolapse, and sometimes renal colic.

Even when the colon is known to be disordered and that disorder seems to be explanation enough of the symptoms, the usual examinations for other conditions should always be made, and will lead in not a few cases to modification of the diagnosis. It is unsafe to give a definite opinion or to embark on a course of treatment without a full consideration of other possibilities. If some other lesion is present, and we have seen above that that is so, or has been, in many of the cases (also in a large number of cases not mentioned in this series whose colitic symptoms were regarded as secondary) it is then necessary, and not always easy, to decide which is the primary or the main causative feature.

A common practical difficulty is the exclusion of appendicitis. In colitis, with even severe spasm, the abdominal muscles are not on guard, and fever is seldom above 99·5° F. Vomiting is unusual, tenderness less localized, and there is not a rising leucocyte count.

The dysenteries are more likely to be confused with 'non-dysenteric' ulcerative colitis, but they leave behind them a state of the colon which may be indistinguishable from functional disorder. The early stage of diverticulosis, if the prediverticular state is extensive, as it sometimes is, may give rise to severe spasm and pain, the cause of which can only be recognized by X-ray examination. I have known a colotomy done for what turned out to be prediverticular spasm. An association with lumbago, sciatica, or herpes would lead to suspicion of diverticulosis, especially if the patient is over 50. Parasitic causes would be discovered on routine faecal examination. The achylic and pancreatic diarrhoeas are more consistent and vary less from month to month than do functional colitic diarrhoeas. Diseases of the womb and adnexa are often coexistent.

Personal inspection of the motions, especially those passed without the use of aperients or enemas, will clear up many difficulties. Of next importance is the use of the sigmoidoscope, in many cases; then X-ray examination of the colon by a barium enema, and if possible with a barium meal also.

The X-ray films may present abnormalities of contours or of mobility which suggest the presence of membranes, adhesions, or kinks. Adhesions are more likely to be present if there has been a previous laparotomy. Caution is

needed before ascribing symptoms to these conditions. If colitic disorder is present it is advisable to give time to careful local and general treatment before coming to a conclusion. If the symptoms disappear, as they often do, then they were not due to the organic deformity. The course of the bowel includes many natural corners and kinks, and such are not of importance unless it can be shown that there is delay in the passage of material and that the delay does not yield to the usual treatment for a sluggish bowel. Adhesions, especially of the omentum, can cause much pain; but adhesions of the bowel, unless they interfere with function, seldom do. I have found few operations less satisfactory than those undertaken for the relief of adhesions in cases in which it could be shown that the intestine was not stretched or obstructed. There is a danger of laying too much stress on any coincident abnormality. A finding is not a diagnosis. Clinical judgement is and always will be the deciding factor.

VII. *Prognosis.*

In nearly all cases the colon and the patient recover if the constipation can be cured without the use of chemical irritants.

The common forms of irritable colon due to constipation and aperients do thoroughly well with correction of habit and suitable treatment. The symptoms vanish and the form and rate of passage of the colon can be shown by later examinations to be normal. Most cases of mucous and muco-membranous colitis with neurasthenia may also recover within two or three months with thorough and whole-time treatment. Cases of colospasm may do well with a good holiday and relief of strain.

If treatment is intermittent and casual, as it often must be for daily workers, these disorders yield with difficulty.

The severe intestinal neurasthenic with membranous crises of long standing tests the perseverance and resource of the doctor. But very few are 'hopeless intestinal defectives' (45), though several months' treatment and encouragement may be needed. I have many times heard years afterwards that patients I had found resistant had eventually completed their recovery by pursuing the advice given. None of these complaints is fatal.

VIII. *Prophylaxis.*

Disorders of the colon arising, as most of them do, from bad habit, in a person nervously predisposed, can be prevented by such hygienic measures as regular meals, exercise, and sleep, a plain mixed diet properly chewed by healthy teeth, and the cultivation of a daily action, avoiding aperient measures other than fruits, plenty of water, and paraffin if needed. Should an action not take place on any day, no pill should be taken that evening; if the bowel is left alone, or at the most lubricated with paraffin, there is usually no harm in waiting two or even three days until a natural action does occur. If a continued

sluggishness of the bowel develops, then the seat of the delay should be determined and suitable treatment applied in order to prevent further disorder.

IX. *Treatment.*

The variety of these disorders and their long course has offered a field for many remedies and régimes. I find notes of no less than fifty-eight measures or medicines recommended, a good number of which I have used. Nevertheless, those which are most useful are much fewer.

The main rules are to allay anxiety, to abolish laxatives and purges, to give a suitable diet, and to regulate rest and exercise. In severe cases it may be necessary to remove the patient for a long period from the surroundings in which the derangement arose.

In cases of colic delay with resulting irritable colon and mild colitis, the patient is erroneously convinced that (1) it is harmful for material to lie in the colon for more than forty-eight hours; (2) if an action does not take place in the morning an aperient should be taken that evening; (3) that a large semi-fluid motion produced by that aperient, to yield which a great part of the colon is emptied, is beneficial; (4) that an ordinary formed motion due to emptying of the lower sigmoid only is not enough; (5) that the abdominal discomfort and loss of vitality are lessened by the constant use of aperients. These opinions I believe to be, in the main, wrong, for reasons stated above.

The advice given as to a regular habit differs according to the seat of the delay, as shown by X-ray examination. In the less common cases, below 3 per cent., in which the hold-up is in the caecum and ascending colon only, some help at first with more than paraffin, e.g. senna, may be needed, but only for a short time. When the sluggishness is general, or mainly in the sigmoid or rectum, the following instructions have been found useful:

An effort should be made at the same time every morning. Remain for ten minutes, trying, say, every third breath, but be careful not to strain so hard as to give pain in the abdomen or in the head.

If there is no result, insert a glycerine suppository, wait ten to fifteen minutes, and then make another effort. If successful, the suppository, when expelled, will be accompanied or followed by a natural action.

If no motion follows, take no notice of missing one day, but carry out the same routine the next day. This time, however, if an action has not been secured after the ten minutes' effort, followed by a suppository and another effort, as described above, then an enema is to be given as soon as possible.

The harm that follows a few days' constipation is exaggerated. Some physicians believe that in health there is none (17, 55), and that if the right food be taken and a regular effort made no further measures should be taken.

A mixed diet is given which differs from an ordinary one in that meat (including the flesh of birds) is reduced, being ordered two or three times a week only, or at the most once a day. Fish, egg dishes, and cream cheese take its place, subject to individual taste. Milk is given in puddings in subjects in whom

an increased weight is called for, but not otherwise. Wholemeal bread is taken, unless the patient dislikes it, with plenty of butter. At breakfast and the mid-day and evening meals either fresh fruit, a salad or cooked green vegetable is taken freely. Subject to these general directions the patient should be advised to aim at eating what is provided and not to consider himself or herself as being on a restricted diet. The habit of picking out this and that is apt to lead to subnutrition.

Acid milk. We usually give also at 11 a.m. 4 oz. of a pure culture of *B. acidophilus* in sterile milk. The culture is standardized to contain two hundred million viable bacilli in a cubic centimetre and is prepared fresh. Lactose is taken freely with meals to furnish a pabulum for the organism. Surgeon-Commanders A. A. Sanders, and T. C. Patterson, R.N. have recently made tests to find out how little of the milk culture and of the lactose was needed to keep the viable organism in the faeces, With an ounce and a half of lactose a day and 100 c.c. of the culture twice a week the stool gave a positive growth of the germ on each occasion. When the culture was given once a week only and the stools examined on the sixth day after, the germ disappeared from the motions. These tests were made on a patient with diverticulitis who was under constant observation.

Plenty of water should be taken at times suitable to the state of digestion, e.g. ordinarily first thing in the morning and with meals; with gastric sub-acidity an hour before each meal; with superacidity and in the obese at the end of a meal, after all solid food has been eaten.

Paraffin is useful, though not always necessary. It should not be taken spasmodically, but in a regular dose of a teaspoonful to a tablespoonful night and morning. If the dose is to be reduced or increased the alteration should be made for three days at a time. The annoyance of its leaking away, apart from motions, may be met by either reducing the dose, giving it in a little warm milk, or immediately after meals. If none of these measures is successful, give in the form of a jelly.

Massage is valuable in this kind of case. The rubber should see the X-ray photographs, especially if the course of the colon is unusual. The caecum or other part of the bowel felt to be loaded should be gently stroked and emptied. In severer cases, when the colon and abdomen generally are tender, and in all cases with diverticulosis, massage is unsuitable.

Regular outdoor exercise is, of course, important, such as walking, croquet, putting, lawn tennis, golf, rowing, or riding, in this order, but must be short of over-fatigue. Special abdominal exercises are redundant for those able to follow these pursuits. For others they are useful, as is faradism to the abdominal muscles. Stimulating baths, vibrations, and external douches, as used at spas, are often of value (16, 58). It is easy to overdo physical treatment in tired people; and patients sometimes ask for more than they are fit for. The body and limbs must be kept warm, the wrists and ankles especially.

In cases of delay and irritable colon, douching is usually not needed, but

when the colon is tender, so that massage is unsuitable, the bowel is then irrigated gently, as described on page 558. If the bowels have not been opened, an enema may be used first.

Adequate physical rest, in milder cases, may be secured by staying in bed for breakfast, resting an hour after the mid-day meal, and retiring early. In severer cases more time, or the whole of the time, will need to be spent in bed.

Mental rest is as important as physical, and can be attained, first, by an adequate examination so that the patient is satisfied as to the nature of the disorder, the fear of worse disease being removed. Upon this depends a reasonable expectation of recovery if the advice be followed and time given. Secondly, the mental disturbance of solicitous and over-anxious friends, with their prejudices about food, fresh air, pills, and potions must be avoided. This is one reason why such patients get better more easily away from home. The mental treatment should include a judicious inquiry into the circumstances in which the nervous disturbance, apprehension, and bad habits arose. This inquiry should not be too deeply psychic; simple explanations are the most satisfying. It is necessary, however, to look at the patient's life as a whole, and advise accordingly for future health. If in any way possible, a proper occupation, a plan in life, should be aimed at for those sufferers who have none; whilst rests, holidays, and some time to follow their own bents should be secured for the overworked and anxious, such as the daughter who is in charge of aged parents. Of drugs, bromide, luminal, and arsenic are used as needed.

Any infective foci will be dealt with, so far as possible, in the mouth, naso-pharynx, adnexa, anus, or elsewhere. Abscesses at the roots of teeth are often unsuspected until revealed by X-rays. Uterine and anal disorders may be a serious hindrance in the treatment of constipation and, especially if concealed, have a potent nervous influence.

In cases with evidence of deficiency of digestive juices, especially gastric or pancreatic juice, appropriate substitutes should be given. Some physicians report also that benefit is obtained from the use of bile as a medicine.

Patients are often sceptical as to the likelihood of cure of the symptoms, and especially of the constipation, but in nearly all improvement in symptoms takes place from the beginning, and a regular habit is shortly established.

The following are some examples of cases in which the alteration in the efficiency of the colon was demonstrated by a further X-ray examination. As regards the severity and duration of symptoms in these and other cases it may be assumed that patients are not sent to a private hospital unless prolonged treatment at home has failed to relieve.

I. 715. ♀ 47. Lassitude, depression, constipation and flatulence. Large residue of barium in colon at 96 hours. After 5 weeks' treatment great improvement, and colon now clear at 48 hours.

II. 176. ♂ 39. Constipation and pain between shoulders. Delay in sigmoid, more than 96-hour residue. After 6 weeks' treatment, clear at 48 hours.

III. 123. ♂ 45. Depression, abdominal dragging and distension. Residue at 120 hours in descending colon and sigmoid. After 2½ months' treatment was well; the bowel was clear at 48 hours.

IV. 378. ♂ 40. Nausea, vomiting, pain, constipation and diarrhoea, flatulence. Large residue at 72 hours. Symptoms disappeared on treatment. The patient followed the instructions given on leaving, and 5 years later re-examination showed that the bowel was still evacuating its residue in a normal time.

Spastic disorder of the colon calls for special measures, in addition to the general ones above mentioned. The mild hypertony found in almost all 'irritable' colons, together with sluggishness, is not included under this heading. The spasticity must affect the whole circumference of the gut, interrupt or deform the column of faeces, and last some time.

If associated with heavy smoking, giving up tobacco may be most of what is needed. Of other hygienic measures, an open-air holiday is most effective. Rougher foods, such as wholemeal bread, raw fruit, salads are excluded, though sieved, well-boiled vegetables and apple purée are allowed. Otherwise the diet is as above mentioned for constipation, with little meat and milk, and plenty of fish, carbohydrate food, and butter.

Of drugs, belladonna is valuable in these patients. Its effect on the bowel was well illustrated in some photographs shown by Dr. Geoffrey Evans to the Association of Physicians (17). In such a patient 7½ to 15 drops of tincture of belladonna in the day, in divided doses, relax the bowel and act as a laxative. Some patients use this remedy regularly for years. It is also recommended by Boas for the chronic forms of mucous colitis. I have found it most useful as a temporary measure. The drug acts on the nerve-endings, but does not directly affect causes lying further back than the neuromuscular mechanism of the bowel. Belladonna is especially useful, with alkalis, in cases of superacidity; and with bromides and valerian for excessive neurosis. Hyoscyamus, in doses of 20 to 30 drops of the tincture, is advocated strongly (75). Intestinal antiseptics, such as Kerol capsules, or 2 gr. of ichthyol in a pill, are sometimes of advantage.

If aperients are needed an emulsion of castor oil, a teaspoonful in a dose, taken each night is valuable, and in some magnesium sulphate has proved successful. In any case the aperient must be taken every day as ordered, not at the patient's discretion. When the bowel opens freely, the daily dose is diminished, with or without the help of a little paraffin until the castor oil or salts are omitted altogether. Some find fruit pastes, made from figs, dates, or prunes, of value. It is best, in my experience, to regard these helps as intermediate steps only. Regular enemas should consist of warm water or normal saline; or an evening injection of four ounces of warm olive oil or paraffin, to be retained all night if possible; or oil and water or camomile enemas. Soap enemas are to be avoided when there is irritation of the bowel.

Severer attacks of *colospasm* are treated by complete rest in bed, hot applications to the abdomen, and warm enemas. Howship's original warm

gruel enema is excellent. Paraffin is given night and morning as recovery takes place. A good dose of belladonna, or even morphia, may be needed, or castor oil containing laudanum. The diet in the attack comprises hot drinks, with thickened soups, water gruel and arrowroot with a little brandy in it on occasion.

When the attack is over a bland diet without fruit, vegetables, peppery food, or savouries is taken at first; then sieved greens are introduced and an attempt made to lead the patient gradually on to an anticonstipation diet with the help of paraffin, belladonna, and the above-discussed hygienic measures.

In cases of *nervous diarrhoea* the use of kaolin, calcium lactate in doses of 10 gr. t.d.s., a holiday with rest as well as exercise, tonic treatment, the omission of fruit and greens from the diet, and encouragement usually yield a good result. To prescribe opium before any engagement is unwise. It does nothing to cure the nervous state, gives no confidence for the future, and is likely to start a habit.

Mucous colitis or catarrh of the colon, in which mucus is passed regularly without membranes and without spasmodic attacks, is a stage further in the development of disorder than the cases of irritable colon mentioned above, and is treated in the same way, except that, in addition, intestinal douches are often used.

Irrigation of the bowel, which was used for intestinal colic by John of Arderne (A.D. 1306–90), has latterly become a therapeutic measure which is undertaken freely, with or without medical prescription, and not always wisely. Douches, when prescribed, should be given gently at a pressure of not more than two feet, with the usual movements and breathings to fill the colon. That the large bowel can be filled completely is shown daily in the X-ray room with the barium enema. Douching should not be too frequent, on alternate days is often enough. Normal saline is probably as good as any of the fluids that have been advocated; the gentle washing of the bowel lining is what is wanted. A reflex secretion of excess mucus may be caused in those who passed none before, which ceases when the gut is more used to the injection. This phenomenon has been sometimes wrongly explained by bath attendants as a washing out of accumulated slime which is later no longer formed. The explanation, though false in the milder cases we are now discussing, may be true for severer types. Intestinal douches may give discomfort, which generally ceases with perseverance: but there are patients whom they do not suit. Chiray and Stieffel imply that douches cause the formation and passage of long membranes, but this has not been so when the irrigation is given as above described. I have not seen advantage and I have seen disadvantage in this disorder from medicated fluids. In ulceration of the bowel, such fluids are sometimes very useful, but we are not now discussing that disease.

Patients are apt to attach undue importance to douching. We use it in most cases of this type, but not in all.

The following cases illustrate the results of treatment:

I. *Mucous colitis with loose motions, but actually colic delay.*

With treatment, material passed more quickly through the colon, whilst motions became less frequent, i.e. normal.

(2114). A woman of 49 complained of bouts of dyspepsia, with loose motions, the first sixteen years ago. Eight years ago mucus appeared first after a course of intestinal douches, which, however, had given relief. Now seldom free from symptoms. The bowels acted two or three times a day after meals. With a barium meal there was great delay, the material not having left the colon at 104 hours. Irregular segmentation and inhibition of the descending colon were shown. The faeces were loose and slimy. Gastric juice subacid. Treated by rest, a dry diet without milk, hydrochloric acid, nux vomica, douches, and a tight bandage to the abdomen. Cream of magnesia was given at first for the dyspepsia.

In ten weeks there were no symptoms; the bowels were regular, the rate of passage less than seventy-two hours, the blood normal and the weight increased by nine pounds. Three years later was keeping well.

II. *Mucous colitis without delay in the colon.*

(2781). A woman of 36 complained of discomfort after food, eructation, tiredness and constipation, sciatica, and 'rheumatic' pains. The appendix had been removed and she had been treated with douches, diathermy, ionization, and vaccines. The gastric juice was normal. The faeces contained mucus and gave a feebly haemolytic *streptococcus*. The barium moved quickly through the colon, causing pain when passing the sigmoid (association of left sciatica with sigmoid irritation). With the enema there was seen irregular segmentation in the transverse colon and inhibition in the sigmoid. There were some calcareous glands in the abdomen.

With rest, tonics, poultices to the abdomen, douches, and an autogenous vaccine, the indigestion cleared up, the bowels acted naturally, and the weight increased by seven pounds. The fibrositis and sciatica were treated at the same time with diathermy and ionization.

III. A case treated successfully without douches.

Mucous colitis, neurosis, anaemia.

(2369). A married woman of 49 had suffered from migraine in youth. Her mother had asthma. For a year she has complained of dyspepsia, headache, constipation, and colicky diarrhoea. Aperients made the symptoms worse. A barium meal showed delay in the proximal colon with increased tone. Red blood cells 3,100,000. She was treated in bed, at first, with massage, paraffin, bromide, and valerian, the inculcation of a daily effort and a lacto-vegetarian diet.

Within five weeks the dyspepsia was in abeyance, the bowels were regular, and the weight increased by five pounds.

In *muco-membranous colitis* we meet a problem which calls for all the resources of experience, sympathy, and patience on the part of the physician, and of patience and co-operation on the part of the sufferer and her relatives. The hygienic measures and mental encouragement above referred to are required *a fortiori*. In advanced cases removal from home and its influence is a first step, with complete rest in bed, and cheerful and confident, but quiet, nurses. The diet ranges from fluids only, through invalid food to plain bland diet, which is given until recovery is in sight, but always aiming at reaching gradually ordinary food with vegetables and fruits. Anaemia must be treated thoroughly.

The attack of pain and distress with separation of membrane is treated as

is an attack of colospasm. Between the attacks and during recovery the treatment is that of catarrhal colitis.

Special physical methods are recommended strongly by various authors, e.g., ionization of salts injected into the bowel and diathermy (71), also galvanism, sinusoidal baths, light and heat therapy, and X-rays (58), and ultra-violet rays (40).

Here is an example of a severe case in which successful treatment was interrupted. *Muco-membranous colitis.* (3053).

A woman of 55, of much mental activity, had had daily actions with a pill which she had taken every night for twenty years. Mucus was passed all this time in quantity, and casts. Severe headaches. For seven years vulval irritation with scarring and excoriation, and urticarial rash on arms, thighs, and elsewhere; much interference with sleep. With exacerbation of mucous discharge worse irritation and headache. The stools and the X-rays showed severe colitis with little segmentation, no pus (see Pl. 34, Fig. 12). With seven weeks' treatment the bowels became regular without aperient other than paraffin, the headaches ceased, sleep was good, six pounds were put on and irritation was becoming less. The period of treatment was wholly inadequate for cure. Her relatives desired her to be treated as long as necessary, but she herself was satisfied that she could go on getting better at home. In the event she became as before.

Many of these patients in each class had been treated by vaccines before coming under observation. In some, vaccines made from faecal cultures, or from the throat, have been used as a part of the régime under my care. Of the value of this treatment I have no evidence to offer. I am not prepared to deny, and if I am sceptical it is because the scientific ground for such treatment is wanting and the clinical evidence is uncertain. This is the experience of many others. Some of the results recorded are perhaps due to protein shock. Vaccines of the coli bacillus are recommended especially in mucous catarrh (9, 18, 23, 72). Most of such recorded successes refer, however, to the more severe forms of infective colitis with which we are not now concerned.

Surgery. In cases of redundancy the constipation as a rule yields to systematic treatment. In a few rare cases operation is needed and will lead to cure. Here is an example:

Severe constipation with redundant sigmoid cured by resection.

(745.) A girl of 21 had suffered from severe constipation for eight years, with bouts of abdominal pain. There was slight distension and tenderness; secondary anaemia. X-rays showed unusual looping of the middle of the descending colon and sigmoid, and irregular segmentation. With careful medical treatment in hospital some improvement but not enough; still periodic constipation with pain. At operation the lower half of the descending colon had a mesentery; this piece of the bowel and the sigmoid rotated on the mesenteric axis producing a partial volvulus. Part of the sigmoid was excised and a lateral anastomosis made. Good recovery with daily action of bowels. Seen ten years later, no recurrence.

Eight years ago I reviewed a small series of cases seeking relief after colectomy or ileosigmoidostomy. Added experience has strengthened the view then expressed that these operations should not be performed unless (i) suitable

and persistent medical treatment has failed, and (ii) sound scientific reasons can be put forward for believing that the operation will benefit the patient. Reason (i) alone is not enough as the symptoms may be aggravated and new ones arise after operation.

The treatment of a sluggish bowel, not otherwise diseased, by colectomy or anastomosis has in general failed, with much unnecessary loss of life. Sir Wm. Hale-White stated many years ago that he had not seen atonic constipation so severe as to warrant surgical interference, and most physicians will agree with him. Lord Dawson says, 'each operation lives its short day and passes into comparative disuse'. Dr. Morgan says that we have at least learned that such surgical experiments do no good, adding 'and after all some wars have cost an equal amount of suffering with no gain at all'.

Colopexy, a milder measure, has recent advocates among surgeons (10), but the evidence is not conclusive. In a review by N. G. Marr of eighteen cases under my care it appears that in six the appendix had been removed on advice and the surgeon had fixed the caecum or colon at the same time. In twelve the patients sought relief of symptoms after colopexy and in eleven of these the colon was still the seat of such disorders as coloptosis, delay, spasm, irritability or diverticulosis. These patients were more fortunate than those short-circuited in that they responded well to medical treatment. They had, however, undergone an operation to fix an organ which was meant to be mobile, without effect; and ineffective operations make such people worse.

It is true that large numbers of these operations have been performed without due investigation or systematic trial of other methods. But not all; and we owe an increasing debt to surgeons for their invaluable help in selected cases of chronic disease of the bowel. Unfortunately even with the added counsel of the physician operations for functional colonic derangements are still unsatisfactory.

The reason is that just as no operation was ever devised which will make a man out of training fit to run a race, so in these patients the bowel is out of training and surgery is not a means of restoring its powers.

The *results of medical treatment* in functional derangements of the colon are in institutional practice good. Various examples have been given above. As a general rule those who are longest under care do the best.

In this series 208 cases underwent treatment for a varying length of time, the average being 6·7 weeks. A general view of the forms of treatment most often used, apart from prescribed mixtures, is given by the following figures:

TABLE VI.

Treatment.	No. of Cases (208).	Percentage.
Bed entirely for some weeks	71	34
Massage	146	70
Intestinal douches	134	64
Bland diet	87	42
Anticonstipation diet with wholemeal bread, fruit, and greens	53	24
Fluid and other diets	10	5
Castor oil	23	11

Of these 208 patients, 2, i.e. 1 per cent., were worse. Nineteen patients, i.e. 9 per cent., were not improved in the time available. One hundred and eighty patients, i.e. 90 per cent., improved greatly or became well while under treatment. All returned to their family doctors with suggested instructions for diet, rest, and general conduct of the case, based on the findings and progress.

These diseases do not kill; but they cause weakness and misery. If, as a profession, we can learn more, and can educate the public, in regard to the hygiene of the colon, a great addition will have been made to human health and happiness.

X. *Summary.*

An analysis is given of the disorders and diseases of the colon which were noted in the examination of 4,000 consecutive patients suffering from various complaints. Among these the disorders of the colon classed as functional are—colonic delay or constipation, irritable colon including nervous diarrhoea, spastic colon and colospasm, mucous colitis or catarrh of the colon, and muco-membranous colitis. Coloptosis with or without gastroptosis or visceroptosis may be present with any of these disorders.

Excluding colonic delay, there were reviewed in this series 242 cases in which the main diagnosis was one of functional disorder of the colon.

After an account of the normal functions of the colon, aetiological factors are discussed, the chief causes of the severer forms of functional disorder being neurosis, constipation, aperients, and past infections. The over-use of aperients is thought to be as potent and frequent a cause as constipation.

In an analysis of 1,000 cases of colonic delay it was found that one-quarter did not complain of constipation. Of the remaining three-quarters, six out of seven were taking aperients, 431 of them every day. In this group colonic disorders were more than double as frequent as they were among the rest.

Some other lesion or irritation of the alimentary system is often present. An example of reflex mucous colitis from a kidney stone is given. Coloptosis is regarded as a secondary result, with colonic delay, of a lowered tone of the intestinal wall.

Careful faecal examination is necessary, but routine bacteriological culture has proved disappointing as an aid to diagnosis or treatment. A diagnosis of auto-intoxication was found to be often misleading.

An analysis of symptoms and signs is set forth, and a description, with plates, of the radiology of the colon, both in the normal state and in functional disease. Notes on diagnosis, prognosis, and prophylaxis follow.

The treatment found useful in each variety of disorder is described, with examples of the results obtained, and a table of the methods most often used.

In over 90 per cent. of cases great benefit or total relief follows adequate treatment.

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DESCRIPTION OF PLATES.

PLATE 30, FIG. 1. To illustrate the slow pendulum movements. The two pictures were taken with 4 seconds' interval. The superimposed tracings of Fig. 1*a* show the change in outline in that time.

FIG. 2. (4984). Shows dropping of the transverse colon at one stage. FIG. 3 shows the same colon 12 hours later. Each photograph was taken in the erect position. In Fig. 3 is seen evidence of excitability of the distal colon.

PLATE 31, FIG. 4. (1770). Photographs of the beginning of a mass movement taken at intervals of 2 seconds.

PLATE 32, FIG. 5. (3513). The sigmoid colon filled with an enema of standard bulk. FIG. 6. The same bowel with an enema of double the bulk, simulating redundancy.

PLATE 33, FIG. 7. Examples of different states of tone of the transverse colon, showing from above below, hyper-, ortho-, and hypotonic bowel.

FIG. 8. (5402). Irritable colon with spasm 24 hours after meal. The lower figure shows the same piece of bowel filled with a barium enema.

FIG. 9. (5514). Barium enema. Spasm of transverse colon probably due to arterial contraction. At the time of this photograph the patient, who was the subject of angina pectoris, was in abdominal pain. The lower picture is of the same colon 6 hours earlier. It shows some inhibition only.

PLATE 34, FIG. 10. (5371). The colon in a case of nervous diarrhoea. The photograph was taken after an evacuation, at 8½ hours after the meal. FIG. 11. The barium enema of the same patient shows that the bowel fills well, with some irritability of the descending colon. (The frequency of the movements ceased under treatment.)

FIG. 12. (3053). Photograph taken during continual contraction and inhibition in a severe case of membranous colitis.

FIG. 13. (1215). Redundant colon. Inhibition of distal part. The sigmoid measured 55 cm. Standard barium enema.

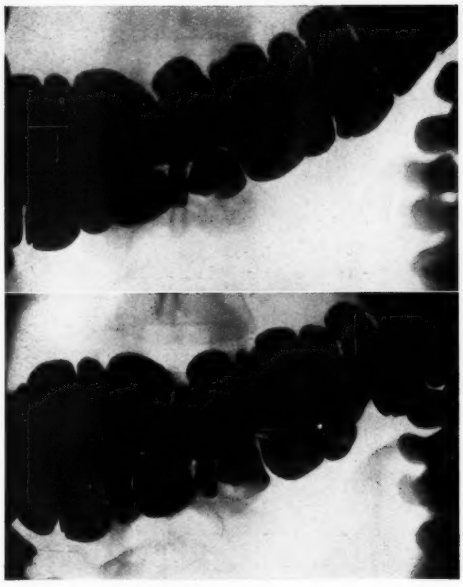

FIG. 1

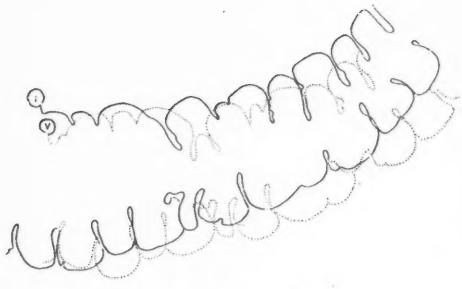

FIG. 1 *a*

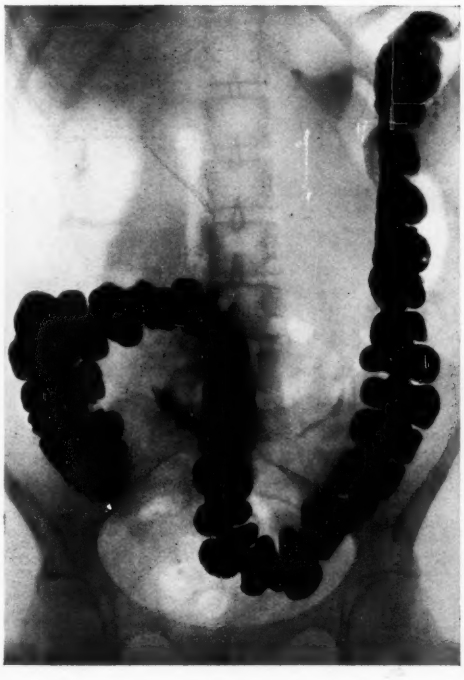

FIG. 2

FIG. 3

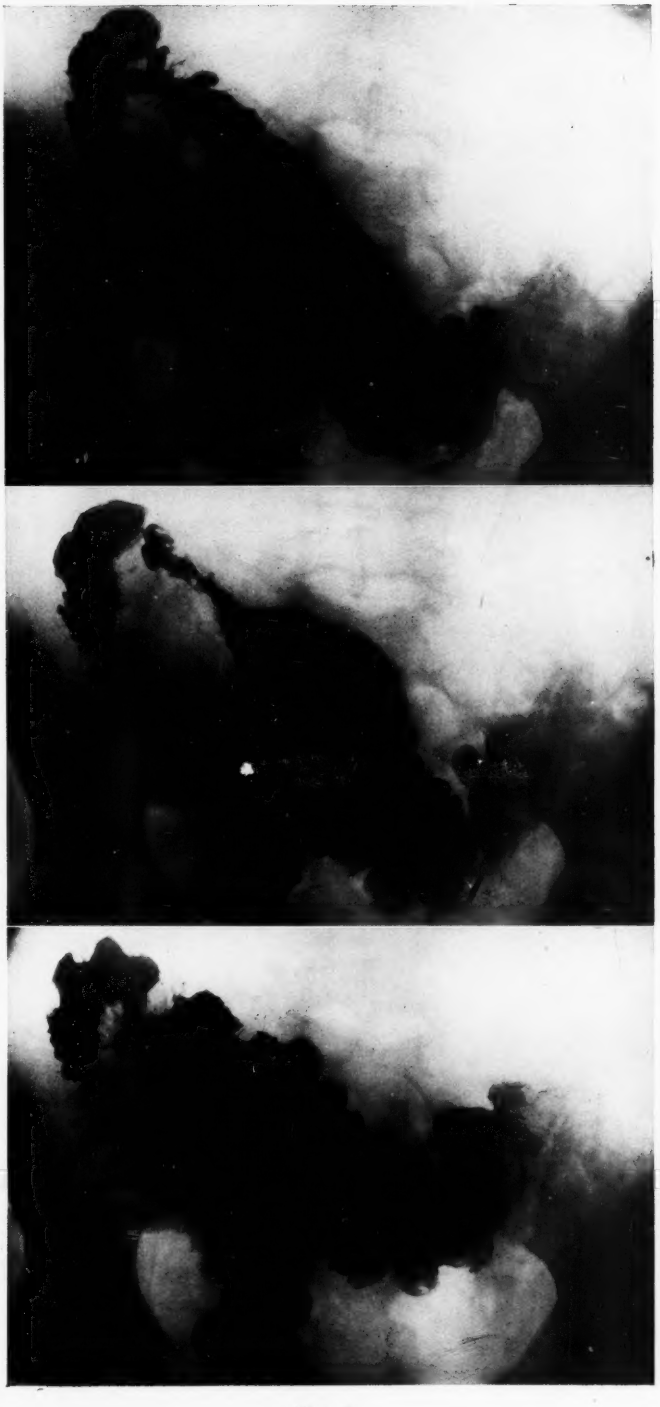

FIG. 4

FIG. 5

FIG. 6

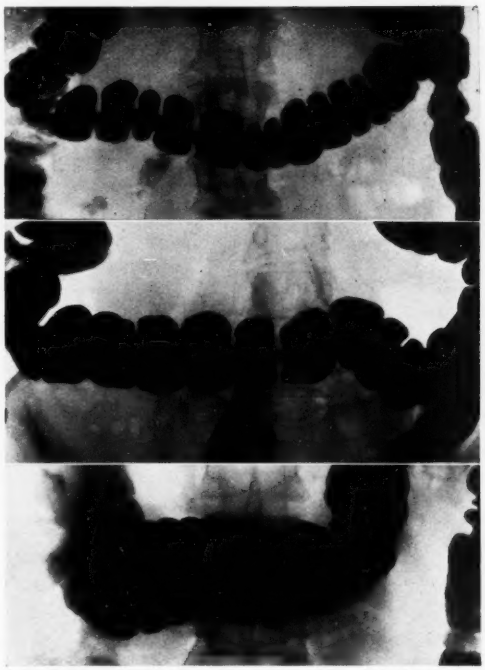

FIG. 7

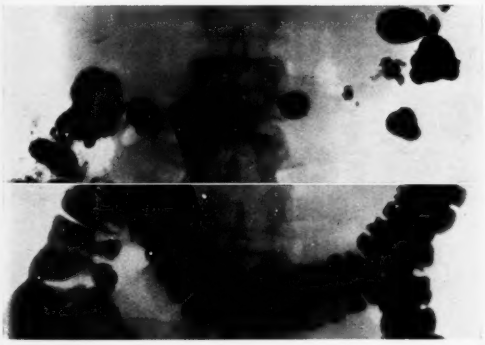

FIG. 8

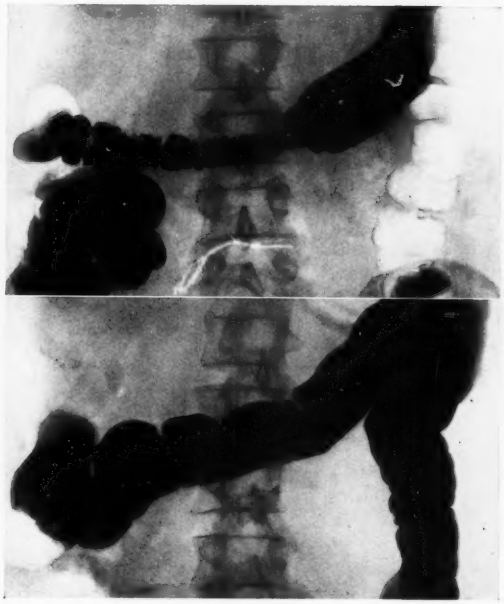

FIG. 9

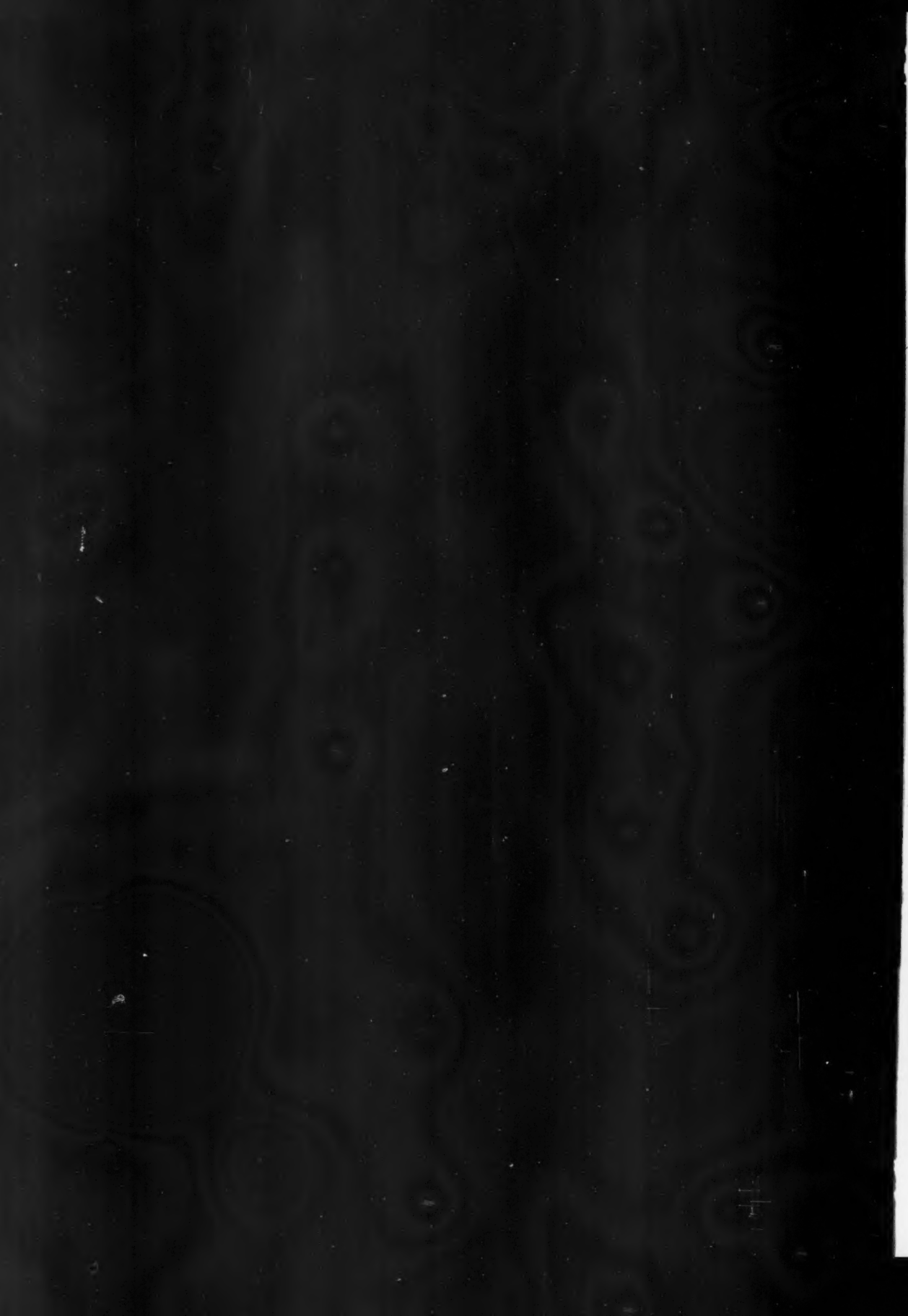

FIG. 10

FIG. 11

FIG. 12

FIG. 13

616.633.815

THE EXCRETION OF CREATININE BY THE HUMAN KIDNEY IN HEALTH AND IN NEPHRITIS[1]

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Introduction.

The history of investigations into renal function may be divided broadly into two main periods, separated by the gradual introduction into physiology of micro-methods of blood analysis. The first period was concerned more especially with the excretion of dyes by the kidney, and with the histological study of their modes of excretion, and dealt also with the concentrations of various substances excreted in the urine.

In the second period micro-analytical methods made possible the numerous attempts to correlate the composition of the urine with that of the blood. This period again, was concerned in its early stages primarily with the concentrations of substances in the urine, and only later with a study of the actual quantities excreted in a given time. These more recent methods also, may be divided into what Starling has called the 'synthetic' and the 'analytic', the former being concerned with a gradual building up of a total of partial renal functions by a study of such preparations as the heart-lung-kidney, and with glomerular punctures, the latter attempting to analyse the complex total function shown by the intact normal kidney acting *in situ*. It is to this latter group that the present work belongs, the findings in the normal subject being applied to the abnormal.

The well-known formulae of Ambard, and the equally well-known theory of Cushny were derived more particularly from a study of concentrations than of the absolute quantities of substances excreted. Although neither of these is universally accepted, nevertheless both have been of enormous value in stimulating investigations attempting to prove or to disprove their contentions.

It was quickly realized, however, that a given kidney did not react in the same manner to a given blood constitution on every occasion. Thus Addis and Watanabe (1) found that with a given urea concentration in the blood-stream, the rate of urea excretion varied very considerably at different times, even when the urine volume was also maintained constant, and this fact was brought as a serious criticism against the Ambard formulae. More recently Rehberg (2)

[1] Received May 8, 1931.

has found that with a constant level of creatinine in the plasma, the rate of excretion of this substance in the urine may vary from 50 per cent. to 200 per cent. of the mean value for a large number of observations. Similar irregularities of behaviour have been frequently observed in the excretion of other urinary constituents.

No other explanation being available, it was not surprising that refuge was taken by some in the idea of a varying vital activity of the renal cells to explain such variations in function. It was not surprising either, that attempts to correlate blood and urine composition by mathematical formulae met with so little success and were widely criticized.

Thus Paulesco (3), and Austin, Stillman, and Van Slyke (4) showed that the Ambard formulae were inadequate to explain the excretion of urea, and Laufberger (5) was unable to apply it successfully to the excretion of creatinine.

Disheartening as was this inability to prophesy the degree of activity of a kidney under given blood conditions from the point of view of renal physiology, the absence of a criterion of normal activity rendered it practically impossible to detect any but the more gross reductions of renal functional ability in diseased conditions. The enormous number of clinical tests of renal impairment which have been introduced of recent years would seem to give eloquent testimony to the inadequacy of the vast majority of them. This inability to assess the degree of functional impairment of a kidney would seem, indeed, to have been one of the greatest hindrances to the progress of knowledge of the course and prognosis of nephritis.

Until this variable activity under apparently similar conditions could be either explained or eliminated, it seemed that little progress would be made in the analytical method of investigation. Of more recent years, however, much work has been done which appears to provide at least a partial physiological explanation of the inconstant activity.

First, it has been shown by direct observation as well as indirect, that the number of renal units functioning at a given time in a single kidney may vary over very wide limits, and is further subject to control in some measure by extra-renal factors. This work will be referred to more fully later. Secondly, a relatively simple means of obtaining a constant reactivity from the kidney, at least for urea, has been worked out by Addis and his associates (6). These workers in a long and careful analysis of the various factors influencing the excretion of urea, have been able to demonstrate that under conditions calculated to stimulate the kidney to maximal activity, the rate of urea excretion for a given kidney becomes directly proportional to the concentration of urea in the blood. The conditions found necessary for this effect are a relatively high blood urea concentration and a large diuresis, which Austin, Stillman, and Van Slyke (4) have shown must exceed 150 to 200 c.c. of urine per hour.

Under these conditions the ratio:

$$\frac{\text{Grams of urea excreted per hour}}{\text{Grams urea per 100 c.c. blood}}$$

becomes almost constant with only small variations for a given individual. Taylor, Drury, and Addis (7) have been able further to show that this ratio is approximately proportional to the mass of functioning tissue, and that therefore the reduction of the ratio below the normal value is an expression of the extent to which the functioning renal tissue has been reduced in the kidney under consideration.

We have in this ratio then, a relatively sensitive means of detecting renal functional impairment, since under the conditions prescribed by Addis, the behaviour of the healthy normal kidney can be foretold, and the extent to which the diseased one falls below normal can be measured.

Considered mathematically, the ratio represents a volume of blood per hour, the volume of blood which would contain the amount of urea excreted in an hour. This ratio has been called by Van Slyke (8) the 'maximum clearance'. It is, of course, not supposed that any given volume of blood passing through the kidney is completely cleared of its urea. Addis and Shevky (9) showed, indeed, that the blood in the renal vein contains only slightly less urea than that of the jugular vein, and Ekehorn (10) has recently reviewed critically the evidence as to blood-flow through the kidney, and concludes that this is many times that required to supply the quantity of urea excreted. The conception of the ratio as a volume of blood 'cleared' of urea is nevertheless of great value in appreciating its significance.

For a healthy man the value of the ratio varies in different individuals from 40 to 55, depending to some extent upon body size. This means that under the so-called 'Addis' conditions the pair of human kidneys will excrete as much urea in one hour as is contained in 40 to 55 times 100 c.c. of blood, i.e. in 4·0 to 5·5 litres, whatever the concentration of urea in that blood may happen to be.

Conditions having been shown to exist under which urea excretion rate bears a simple linear relation to blood urea concentration, it seemed of great interest to study the excretion of other urinary constituents under the same constant conditions, not with a view to introducing yet other tests of renal function, but to attempting to discover what other substances were excreted in the same manner, and the way in which their excretion was affected in nephritis.

Various considerations which need not be entered into here led to the choice of sulphates and of creatinine for primary study. In the present paper only the results obtained with creatinine will be considered.

The Excretion of Creatinine.

Numerous workers have commented on the relative constancy of the excretion rate of creatinine over a period of time, and have shown that it is unaffected by changes in the urine volume and by water diuresis or other diuretics (Van Hoogenhuyze and Verploegh (11), Klercker (12), and Shaffer (13)).

On the extent to which creatinine in its excretion agreed with the formulae of Ambard, no unanimity could be reached. Fontayne and Inglebricht (14) believed that it did, and considered the constant in the formula to be about half that for urea. They further held that creatinine output was independent of the blood creatine concentration. Their experiments were somewhat unsatisfactory, however, in that the blood creatinine concentration was only varied between narrow limits. Cantinieaux (15), on the other hand, was less certain of the agreement. He held that in nephritics the Ambard constant for creatinine was about a third of that for urea, but considered that its excretion was dependent on the blood creatine concentration, as well as on the blood creatinine. He was inclined to agree with Laufberger (5) that creatinine, at least, does not obey the Ambard laws. Heesch and Tscherning (16) concluded from their experiments on dogs that the kidneys are but little concerned in the control of creatinine excretion, this being mainly determined by back flow from a store in the general tissues, without reflected change in the blood.

In view of the earlier mentioned findings of Rehberg (2) that under ordinary circumstances a constant level of creatinine in the blood does not lead to a constant excretion rate of this substance in the urine, the discrepancies and disagreements among the above-mentioned workers are not surprising. In considering the problem, also, the contentions of Behre and Benedict (17) must be borne in mind. These workers were unable to find evidence of the presence of more than a very small trace of free creatinine in the blood, and suggested that the chromogenic substance was one with properties different from creatinine. They further suggested that creatinine was formed from the creatine in the blood. Support is given to the idea of other substances being responsible at least in part for the picrate colour reaction by the findings of Jaffe (18), Feigl (19) and others that acetone, methylglyoxal, pyruvic acid and numerous other substances may give a similar colour reaction with alkaline picrate in the cold. The bearing of these points on the present problem will be further discussed later in the light of the results obtained.

It was decided to study the effects of variations in the plasma creatinine concentration on the rate of excretion under the constant conditions devised by Addis.

Methods.

The subject for the whole series of these normal experiments was the same (C. L. C.). As far as possible the same routine was employed in each experiment. The subject was permitted a small breakfast (8.30 a.m.), but tea, coffee, cocoa, and tobacco were rigidly excluded from the period before the experiment, these having been shown by Addis and Drury (21) to raise the urea clearance.

At 9.30 a.m. about 1,000 c.c. of water were drunk, containing 20 grm. of urea and a variable amount of creatinine. At 10 a.m. the period of rest was commenced, the position adopted being semi-recumbent in a comfortable arm-

chair in a warm room. That a constant position is highly desirable has been shown in a paper published since these experiments were completed, in which it was found that considerable variations in renal activity may result from change in posture (22). At 10.30 a.m. about 500 c.c. more water were drunk, preferably slightly warmed, and the bladder was emptied as completely as possible, the exact time being noted. At 11 a.m. a sample of blood, usually about 12 c.c., was withdrawn from an antecubital vein. Coagulation of this was prevented by receiving it into 0·25 c.c. of water containing 50 mg. of crystalline sodium citrate. In the subsequent analyses allowance was made for this slight dilution of the blood. At 11.30 a.m. the bladder was again emptied completely, the whole sample of urine excreted during the previous hour being preserved and its volume measured.

All experiments were performed during the morning hours because MacKay (23) has found that renal activity is then relatively more constant than later in the day. No ill effects were observed from the doses of urea and creatinine except for some marked pain in the renal region on one occasion during the height of the diuresis, a pain which persisted for two or three days. It is of some interest, however, that on several occasions a definite uraemic odour could be detected in the breath for some hours after the urea ingestion.

The Analyses.

Urea in blood was estimated by the usual soya bean and aeration method, using duplicate samples of 3 c.c. of whole blood. The ammonia was drawn over into N/50 acid, and the back titration carried out with CO_2-free soda of approximately N/50 concentration.

Urea in urine was estimated by the same method as for blood, $\frac{1}{2}$, 1, or 2 c.c. being used according to the degree of dilution. All estimations were made in duplicate.

Creatinine in urine was determined by the usual method of Folin (24) standard solution and urine solution being prepared so as to give approximately the same intensity of colour. For this, as also for the plasma creatinine determinations, a Dubosq colorimeter was found satisfactory. Direct proportionality between colour and concentration was assumed.

Creatinine in plasma appeared to be the estimation most liable to error, partly from the uncertainty of the identity of some of the chromogenic substance, but more particularly from the difficulty of comparing accurately the weak yellow colours obtained with the lower concentrations. In order, therefore, to eliminate all tendency to bias in comparing the colours, it was made the invariable rule to estimate plasma concentration before the urinary creatinine.

A slightly modified Folin method on a Folin-Wu filtrate was employed. Plasma was considered preferable to whole blood owing to the doubts which have been cast on the accuracy of the method when applied to whole blood (Hunter and Campbell (25)). Picric acid was purified by Folin's original

method (26), and using his test for purity gave a figure of 20 : 13·4. The Newcomb factor (27) was 0·12. The same sample of picric acid was used for the whole series of estimations on both urine and plasma. A constant concentration was obtained by making up accurately by weight a 1 per cent. solution at frequent intervals from the dry stock kept in the dark (Wilson and Plass (28)). For each estimation a series of three standards was prepared, calculated to cover the expected range of creatinine concentration and differing from one another by the equivalent of 0·3 or 0·6 mg. per 100 c.c. of plasma. In no case did the difference in colour between standard and unknown exceed 10 per cent. (2 mm.). The creatinine concentrations were read off from a curve prepared by direct observation, this being necessary owing to the wide deviation from the direct proportionality relation at these low concentrations of creatinine (Hunter and Campbell (29)). In some cases colour comparison was made against two standards of different strength, and in these the values for plasma creatinine obtained did not differ by more than 1 to 2 per cent. In all cases the mean of twenty readings, ten on each side of the colorimeter, was taken.

Results.

The conditions prevailing in this series of experiments have been those shown by Addis to produce constancy of behaviour of the kidney as regards urea excretion. The volume of urine has in all cases been large, in only one instance less than 400 c.c. per hour. As far as possible it was sought to make plasma creatinine the sole variable factor. The range of concentrations studied lay from the normal of 1·2 mg. per 100 c.c. to 8 mg., the variations being obtained by altering the amount of creatinine ingested with urea at the commencement of the experiment. It was found that 2 grm. of creatinine taken by mouth raised the plasma creatinine by about 2 mg. per 100 c.c. and proportionally for other quantities. The greatest amount taken at one time was 7 grm. Ingestion by mouth was considered to be preferable to intravenous injection, not only because of the undesirability of the latter on general grounds, but also because Heesch and Tscherning (16) have shown that after intravenous injection of creatinine there occur large and rapid changes in plasma creatinine concentration until an equilibrium between blood and tissues is obtained. After oral administration the change of concentration is much slower (Rehberg (2)).

The results obtained are expressed graphically in Fig. 1, in which plasma creatinine concentration has been plotted against the amount of creatinine excreted in one hour in the urine.

From the results as there plotted, the following facts would appear to be demonstrable:

(*a*) The reaction of the kidney to change in plasma creatinine concentration is approximately constant under the conditions of the experiments.

(*b*) At plasma concentrations exceeding the normal there exists a direct linear relation between the concentration and the amount of creatinine excreted

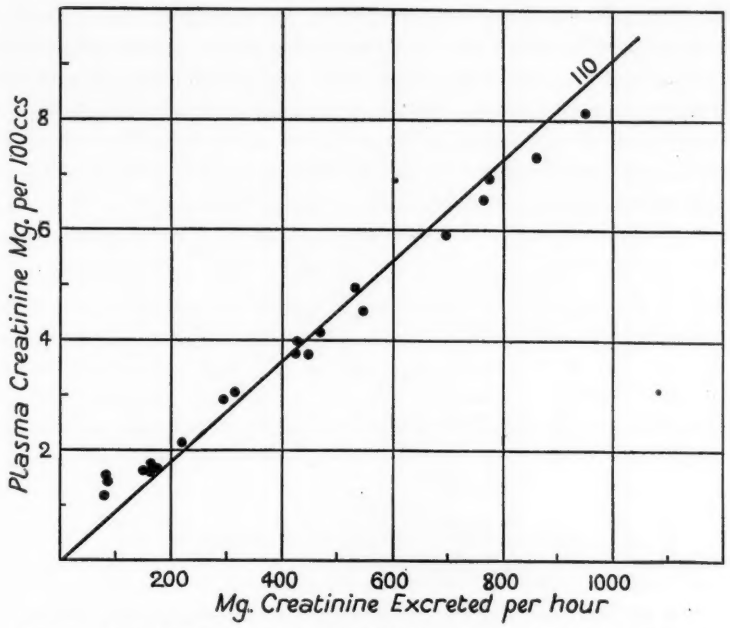

FIG. 1. Creatinine Excretion in Normal Subject (C. L. C.) under conditions of Maximal Activity.

TABLE I.

Creatinine Excretion in Normal Subject (C. L. C.).

Exp. No.	Vol. of Urine.	Plasma Creatinine Mg. per 100 c.c.	Urine Creatinine Mg. per 100 c.c.	Creatinine Excretion per hour in Mg.	Creatinine Clearance.	Corrected Creatinine Clearance.	Blood Urea Mg. % c.c.	Urea Excretion Grm. per Hour.	Urea Clearance.
1	656	1·20	12·3	80·7	66·9	115·3	—	—	—
2	662	1·44	12·9	85·4	59·3	90·8	—	—	—
3	664	1·56	12·38	82·2	52·8	77·6	—	—	—
4	312	1·65	54·6	170·3	106·0	148·0	—	—	—
5	593	1·68	26·0	152·0	91·7	128·8	—	—	—
6	560	1·71	29·4	164·7	96·3	136·1	—	—	—
7	524	1·75	31·3	160·0	93·7	131·2	—	—	—
8	538	2·20	40·7	219·0	100·0	128·8	74·7	3·05	40·8
9	438	2·98	68·36	299·4	100·5	120·8	81·6	2·96	36·0
10	478	3·05	64·5	308·3	101·0	121·0	74·9	3·16	42·2
11	442	3·76	101·6	449·0	119·4	137·7	75·7	3·19	41·5
12	558	3·79	73·9	412·7	111·0	125·4	90·1	3·68	41·1
13	490	3·91	87·2	428·0	109·2	125·0	—	—	—
14	791	4·16	58·7	464·7	112·0	127·0	83·0	3·55	42·7
15	564	4·54	96·78	545·9	120·2	135·1	72·0	3·24	45·0
16	540	4·90	98·85	534·0	109·0	121·4	86·2	3·20	35·6
17	762	5·88	91·44	696·8	118·4	129·5	75·4	3·46	45·7
18	666	6·57	114·8	764·4	116·3	125·9	76·2	3·28	43·0
19	716	6·88	108·5	777·0	113·0	121·8	75·8	3·55	46·7
20	661	7·29	130·2	860·6	118·0	126·6	82·6	3·37	41·1
21	833	8·06	114·1	950·5	117·7	125·7	85·0	3·33	39·2

in unit time. Whilst this work was being done MacKay and Cockrill (30) published a paper in which they demonstrated a similar linear relationship for creatinine excretion in rabbits under Addis conditions. The present results would appear to confirm their findings, at the same time extending them to man.

It appears, however, that points obtained when the blood creatinine is normal do not necessarily lie on the general curve, but give a rather lower clearance value.

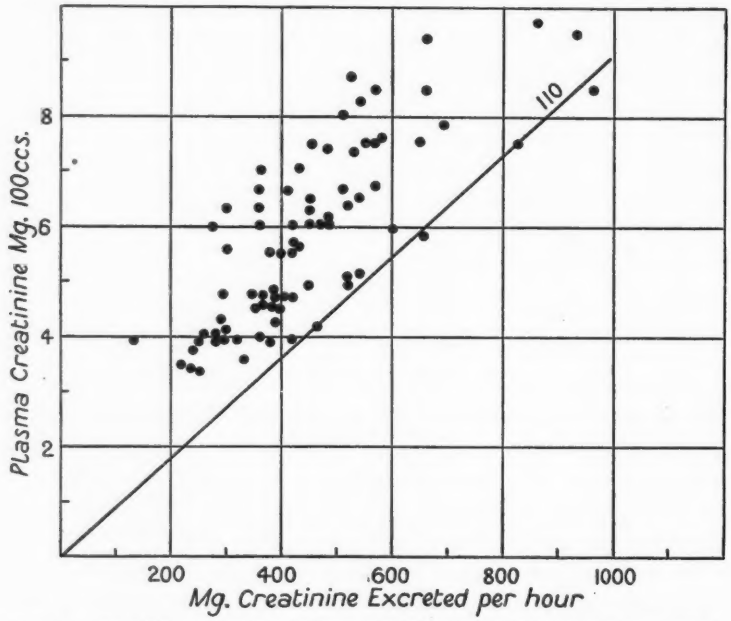

FIG. 1*a*. Creatinine Excretion in Normal Subject (P. B. R.) under Uncontrolled Conditions (modified from Rehberg, *Biochem. Journ.*, 1926, xx. 454).

(*c*) The points lie about a line which has a definite tendency to cross one drawn so as to cut both abscissae and ordinates at zero. They lie about a line which, if produced, cuts the ordinate at a point corresponding to approximately 0·5 mg. of creatinine per 100 c.c. There appears to be a kind of threshold at this point. This fact is perhaps better demonstrated if the ratios $\frac{\text{Mg. creatinine excreted per hour}}{\text{Mg. creatinine per 100 c.c. plasma}}$, i.e. the creatinine clearances, are calculated, Table I. These tend to rise progressively with rising plasma creatinine from 91·7 at 1·68 mg. per 100 c.c. to 118 at a concentration of 8·06 mg. per 100 c.c. If, however, 0·5 mg. be subtracted from the estimated creatinine concentration and the 'corrected clearances' are recalculated, it will be seen that there exists relative constancy of the ratio throughout the range of concentrations studied above normal levels. This 'corrected clearance' averages about 124. We may say, therefore, that under these conditions all creatinine in excess of 0·5 mg. as estimated is excreted in a constant manner, the amount excreted in one hour

being that contained in 124 times 100 c.c., i.e. in 12·4 litres of plasma, whatever the concentration in that plasma may be.

(*d*) In the last column are given the clearance figures for urea obtained simultaneously with those for creatinine. From these a further fact may be observed. The 'corrected clearance' for creatinine is approximately three times as large as that for urea, the figures averaging respectively 124 and 41·8. In other words, for a given blood concentration of both substances, creatinine would be excreted three times as rapidly as urea.

In this series the urea clearance figures show definitely larger variations than do the creatinine clearances. These urea variations are larger than were obtained by Addis in his experiments, and may therefore be due to inadequate standardization of the conditions. They are, however, of the same order as those obtained by Van Slyke, &c. (8). The results suggest that the urea clearances are rather more sensitive to small changes in the conditions than are the creatinine clearances.

Discussion of Normal Creatinine Excretion.

It is of interest to compare the curve shown above with the figure given by Rehberg (2) (p. 454) in which creatinine clearances have been estimated, although under a different name (Fig. 1*a*). Rehberg's results differ from the present ones in that no attempt appears to have been made to obtain constancy of, or maximal degree of renal activity. Under his uncontrolled conditions Rehberg found that the ratio $\frac{\text{mg. creatinine excreted in one minute}}{\text{mg. creatinine in one c.c. of plasma}}$ varied from 60 to 200 per minute in the same subject. These figures correspond to hourly clearance figures of from 36 to 120. In the results here presented, however, the uncorrected clearance for supra-normal creatinine concentrations has appeared fairly constant, tending only slightly to increase with rising plasma concentration. Compared with the figures of Rehberg, the present curve shows practically maximal excretion at every point.

Now if the figures obtained by Addis and Drury (31) for urea excretion are examined, it will be seen that a precisely similar wide variation in renal activity exists to that obtained by Rehberg, whilst the results also given in the same paper for urea excretion under conditions designed to yield maximal activity, show a similar relation to that shown in Fig. 1. In both the excretory activity is maximal.

It would seem therefore that those conditions which result in constant maximal excretion of urea, viz. raised blood urea and large diuresis, also lead to constant maximal excretion of creatinine. The change brought about in the kidney is thus not one which affects urea excretion alone.

The fact that under the influence of urea and a large diuresis, the kidney appears to react in a constant and regular manner to the concentrations of both urea and creatinine in the circulating blood, would seem to be of considerable

importance as much from the clinical as from the purely physiological standpoint. As to the mechanism by which this constancy of reaction is achieved, we can at present make no more than a guess. It is possible that urea stimulates to full activity the secreting power of the renal tubule cells for this substance, but it seems unlikely that it would do so also for creatinine. To the writer, therefore, a second possibility appears more probable.

It has for some time been realized that under ordinary conditions only a fraction of the available glomeruli are functional at any one time. Richards and Schmidt (32), observed this fact directly in the kidneys of frogs, and found the number variable. They state, indeed, 'these observations provide evidence to reintroduce into considerations of renal physiology the conception of Hermann . . . that the extent of filtration surface in the kidney is variable, and a factor which must be of major importance in the adjustment of renal function to excretory requirement' (p. 207). Hayman and Starr (33) have obtained indirect evidence that under ordinary conditions, from 56 to 89 per cent. of the glomeruli in the kidney of a rabbit may be active, and they further remark that wide variations in the number of open glomeruli occur spontaneously, and may be produced experimentally, and that all, or nearly all, the glomeruli are open during the action of caffeine and of salt solution. Khanolkar (34) has also obtained similar indirect evidence of varying glomerular activity in mammals.

As it is now believed that all the blood passing to the tubules has first passed through glomeruli (evidence reviewed by Huber (35)), it must be assumed that partial activity of the glomeruli is indicative of partial activity of the tubules of approximately the same extent, a suggestion made earlier by MacCallum (35*a*). This being so it must follow that whether the filtration-reabsorption theory or the secretion theory be the true one, partial activity of the glomeruli will lead to submaximal excretion of creatinine.

Now it has been shown by Richards and Schmidt (32), that under the influence of urea all, or nearly all, the glomeruli could be brought to a state of full activity. It would seem not improbable that a similar state has been brought about in the experiments on man described in this paper, and this would account in part for the constancy of reaction under such conditions. It must be mentioned, however, that Ekehorn (10) is unwilling to believe that maximal activity can ever be obtained. From his experiments he concludes, 'the glomerular apparatus is constructed on so liberal a scale that it never is, and cannot possibly be fully utilized by the organism' (p. 298). It seems to the present writer extremely unlikely, however, that a kidney should be unable to call upon at least the great majority of its endowment of renal units in a moment of stress.

It is of interest to consider the present findings from another standpoint. Rehberg (2) has put forward the interesting suggestion that creatinine excretion is a measure of the volume of the glomerular filtrate. In doing so he assumes tentatively that creatinine is excreted into the tubule entirely through

the glomerulus, coming through as a constituent of the ultrafiltrate produced there, in the same concentration as it exists in the blood. Adopting the filtration-reabsorption theory, he supposes water but not creatinine to be reabsorbed in the tubules. If then the plasma creatinine concentration and the amount of creatinine excreted in unit time be known, simple division yields the volume of glomerular filtrate which must have been formed to contain the quantity of creatinine found in the final urine. Actually the 'creatinine clearance' is numerically the same figure. If we accept this somewhat speculative, but nevertheless highly stimulating suggestion of Rehberg's, we must conclude that in the present series of experiments the ultrafiltrate has been produced in the glomeruli at an almost constant rate of something over 10,000 c.c. per hour, and that about 95 per cent. of the fluid has been reabsorbed. It is not proposed to consider here the evidence for and against Rehberg's suggestion. This has been done ably and at length by Ekehorn (10).

It has already been mentioned that the creatinine clearance tends to rise with increasing plasma creatinine concentration, and that approximate constancy of the value is obtained if 0·5 mg. is deducted from the plasma creatinine figure found. Two possible explanations of such a fact can be brought forward. First, that there exists at this point of 0·5 mg. per cent. a threshold value for creatinine, and that only amounts in excess of that figure are available for determining excretion by the kidney. Secondly, that a colour equal in intensity to that given by 0·5 mg. of creatinine is given by other chromogenic factors present in the plasma. Although no definite evidence is here adduced, the latter view appears to the writer to be the more probable.

Behre and Benedict (17) have brought forward evidence to show that the free creatinine present in blood is only a small fraction of that estimated by the Jaffe alkaline picrate colour reaction. It is not without interest to consider briefly their findings.

A. They state that there exists in blood a substance differing from creatinine in that it reacts with picric acid strongly in presence of sodium carbonate. It would seem possible that the cause of this is the presence of substances such as glucose, pyruvic acid and diketo-piperazides which have been shown by Brand and Sandberg (20) to react with picric acid especially after treatment with sodium carbonate.

B. Unlike creatinine the chromogenic substance in blood is not destroyed by heating for one hour with 2 per cent. caustic soda. It is known, however, that under such treatment glucose forms substances giving similar colour reactions to creatinine. It seems not unlikely, therefore, that such substances replace the lost chromogenic power of the destroyed creatinine. Patch and Rabinowitch (36) have, moreover, found that in some cases all the blood creatinine could be destroyed by heat, in others only a part.

C. In beef blood only from 30 to 50 per cent. of the total blood 'creatinine' is removed by kaolin, which will remove real creatinine quantitatively from dilute solutions. Such a finding would correspond to 0·6 to 0·8 mg. per

cent. of irremovable creatinine, a figure not far removed from the approximately 0·5 mg. considered above to be immune from excretion by the kidney.

D. Their finding that kaolin does not remove 'creatinine' from protein-free filtrates cannot readily be explained, however, on the present assumption.

The question of the precise amount of 'inert' creatinine in the plasma must await further research. The fact that in the present experiments the kidney has reacted in a constant manner only to that creatinine present in excess of 0·5 mg. per 100 c.c. suggests strongly that this quantity of chromogenic substance is present in an inert form.

Since this conclusion was reached from purely physiological evidence, and since the above was written, the important work of Gaebler (45) has been brought to the notice of the writer. Gaebler has been able to isolate from human blood 0·4 to 0·6 mg. of true creatinine per 100 c.c. Allowing for somewhat incomplete recovery these figures agree well with the requirements from physiological evidence. Gaebler claims that the creatinine is present in a non-chromogenic form which is readily converted into true creatinine. The conclusions reached by Gaebler from chemical evidence would appear to agree with the findings of the present writer if it is assumed that the kidneys react to Gaebler's 'non-chromogenic creatinine' as though it were true creatinine. His findings go far to effect a reconciliation between the present work and the results of Behre and Benedict with which it appeared to be in conflict.

The constancy of behaviour of the kidney to creatinine in the normal subject, provides a physiological background for studying the behaviour of the kidneys in the pathological subject.

The Excretion of Creatinine in Nephritis.

It was remarked in the introduction to this paper that inability to prophesy the activity of a kidney under supposedly constant blood conditions rendered it practically impossible to determine to what extent renal function had been rendered subnormal by disease. The constancy of urea excretion obtained by Addis and by Van Slyke has been made the basis of a test for assessing the degree of impairment of renal function, since it has been shown that in nephritics, and in experimental conditions in which the amount of functional renal tissue is reduced, the urea excretion as judged by the urea maximum clearance, i.e. the clearance under conditions of maximum activity, is also reduced, this reduction being proportional to the degree of reduction of functioning renal tissue (Addis, Watanabe, and Oliver (37), Addis and Watanabe (38)). It seemed, therefore, of considerable interest to attempt to discover whether the ability to excrete creatinine was also reduced in like measure in individuals suffering from nephritis, since constancy of excretion in the normal subject could now be obtained.

Rehberg (39) and Holten and Rehberg (40, 41) have already shown that the 'glomerular filtrate' or 'creatinine clearance' is markedly reduced in

nephritis, but these workers did not attempt to compare this reduction with the ability to excrete urea measured in the same way.

A series of investigations has therefore been carried out in which creatinine excretion ability has been compared with urea excreting power in the same individual. The conditions of these experiments were the same as those employed on the normal subject in the first part of this paper, with the difference that the majority of the nephritics studied were resting in bed during the experiment, and had had no breakfast, and that in one or two cases in which the volume of urine was small, a two-hour excretion period was used, the blood being drawn in the middle of the period. In some cases in which the efficiency of the kidney was getting progressively worse it was possible to obtain figures at different degrees of renal impairment in the same subject.

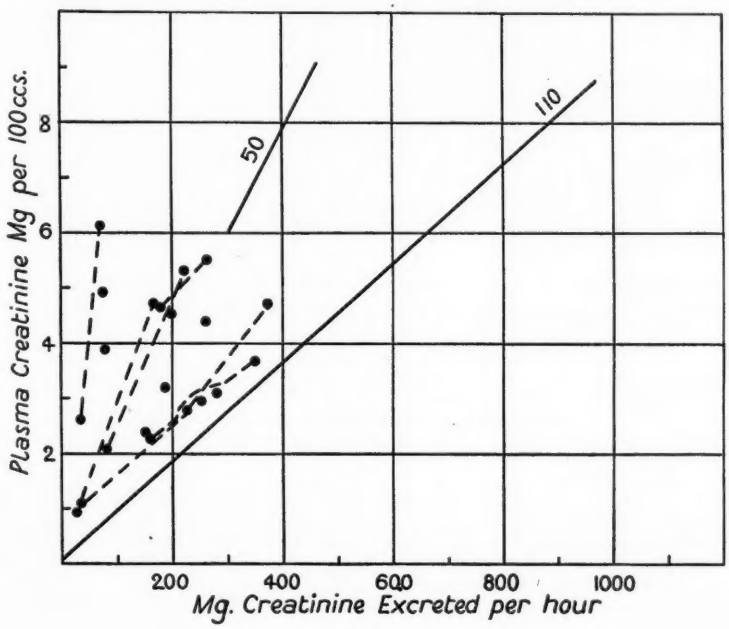

FIG. 2.

The results obtained are set out in tabular form below, Table II, and graphically in Fig. 2, the same scale as was used for Fig. 1 being employed.

It will be seen that the ability to excrete creatinine is markedly reduced in the cases examined, and this reduction was found to bear a rough relation to the clinical estimate of the severity of the lesion. In the figure broken lines join points obtained at different creatinine concentrations in the same individual. Although the evidence is less convincing than in the normal subject it would seem highly probable that a linear relation between plasma creatinine concentration and creatinine excretion rate exists, the line representing this relation becoming steeper as the renal function is progressively impaired. The

extent to which the broken lines in the figure radiate from a common origin is an expression of this fact, although it must be borne in mind that renal efficiency has probably deteriorated during the interval between the experiments on a given individual, evidence of this being given in the fall in the urea clearances in several cases. The creatinine clearance is an index of the steepness of the line expressing this relation, just as the urea clearance is an index of the steepness of the line relating blood urea concentration to urea excretion rate.

TABLE II.

Creatinine Excretion in Nephritic Subjects.

Subject and Disease	Volume of Urine in 1 hr.	Plasma Creatinine Mg. % c.c.	Urine Creatinine Mg. % c.c.	Creatinine Excretion Mg. per Hour.	Creatinine Clearance.	Corrected Creatinine Clearance.	Urea Clearance.
Ward (albuminuria)	337	2·95	75·5	254·4	86·2	103·9	30·0
Reynolds (chronic nephritis)	77·5*	4·64	228·5	176·9	38·1	42·8	9·28
,,	168	5·51	153·3	257·5	46·7	51·4	12·7
Carthew (chronic nephritis)	424	1·11	7·6	32·2	29·0	52·8	27·1
,,	471	4·70	69·8	370·0	69·9	78·3	—
,,	471	2·72	42·24	199·0	73·1	89·6	23·4
Oliver (chronic nephritis)	670	3·67	52·05	349·0	95·0	106·7	35·6
,,	419	2·27	37·66	156·8	69·0	88·6	25·4
Blunt (pyelonephritis)	144	3·14	194·0	280·0	89·8	106·1	26·5
Freeman (hydraemic nephritis slight oedema)	61*	2·59	60·53	36·9	14·3	17·66	6·53
,,	50*	6·10	145·6	72·8	11·9	13·0	4·47
Carpenter (chronic nephritis)	184	2·05	44·11	81·1	39·6	52·3	22·0
,,	190	5·33	115·6	219·7	41·2	45·5	17·2
Longford (subacute hydraemic nephritis)	122	0·94	23·84	29·2	31·1	66·3	16·55
,,	124	4·70	133·7	165·8	35·3	39·5	9·5
Eggleton (albuminuria)	432	3·17	40·81	186·7	58·9	69·9	23·5
Rowney (albuminuria)	216	2·32	71·12	153·6	66·2	84·2	28·8
Shewell (prostatic obstruction)	189 (Catheter)	4·53	101·8	192·3	42·5	47·7	20·3
Antell (subacute nephritis)	55·5* (Catheter)	4·90	135·0	75·2	15·3	17·05	6·74
Ingram (diabetic gangrene)	105	4·36	248·0	260·4	60·4	68·2	21·9

* Strictly speaking, the urine volume in these cases is too small for the results to be considered as maximum urea clearances, although a large volume of water had been ingested. To avoid complications in considering the results they have been included without allowance for the smallness of the urine volume. For the effects of restricted urine volume on urea excretion see Möller, McIntosh, and Van Slyke (8).

A clearer appreciation of the relationship between renal damage and the impairment of creatinine excretion may be obtained from Figs. 3 and 4. In these the maximum clearance for urea has been taken as an index of reduction of renal tissue. In Fig. 3 it is plotted against the creatinine clearances (uncorrected), and it will be seen that though some relation exists, there is considerable scattering of the points. It was, however, found in the normal subject

that when plasma creatinine is variable, much greater constancy of the clearance is obtained by assuming that about 0·5 mg. of the estimated creatinine is inert, and subtracting this figure from the values estimated. In Fig. 4 the 'corrected clearances' so obtained are plotted against urea clearances, and it will be seen that a much closer relationship then exists between the two.

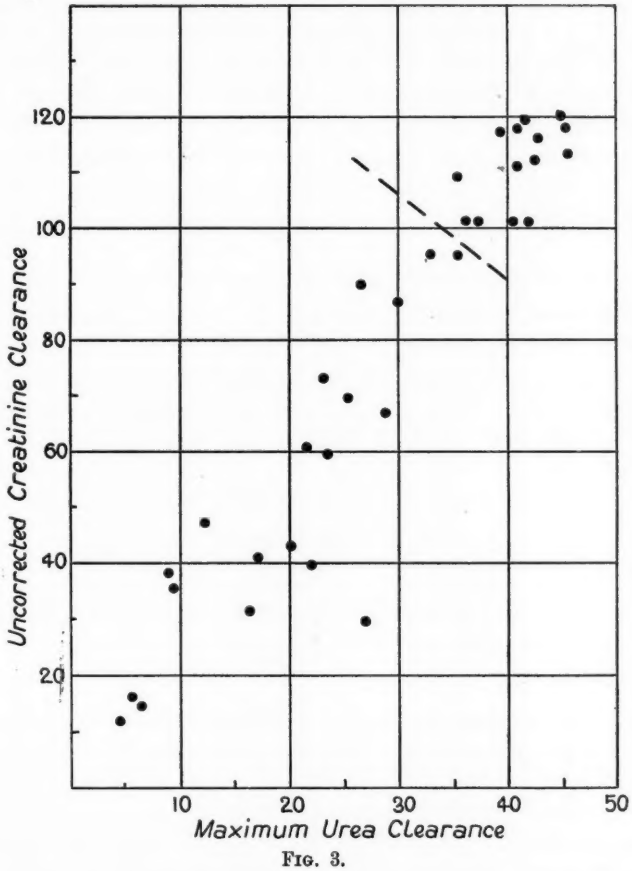

FIG. 3.

Two points only deviate seriously from the general line (*a* and *b*). These two points, however, represent the only two observations made in which no creatinine was given by mouth, and it has already been remarked that creatinine clearances obtained with normal blood creatinine concentration tend to be markedly below those obtained when the concentration is artificially raised. This fact would appear to be the basis of the two discrepant results.

There is, of course, strictly speaking, no justification for assuming that the supposedly inert fraction of 0·5 mg. found in the subject C.L.C. can be applied to nephritic subjects. If there are actually present non-creatinine chromogenic substances in the blood-plasma, the amount of these will presumably be

different in different individuals, and especially in those with nephritis. The fact that better correspondence with the urea values is obtained by deducting this fraction does nevertheless tend to suggest that a nearer approach to the true creatinine concentration is thereby obtained. It suggests also that, if the true creatinine concentration were known in each case, the correspondence with the urea values would be still closer.

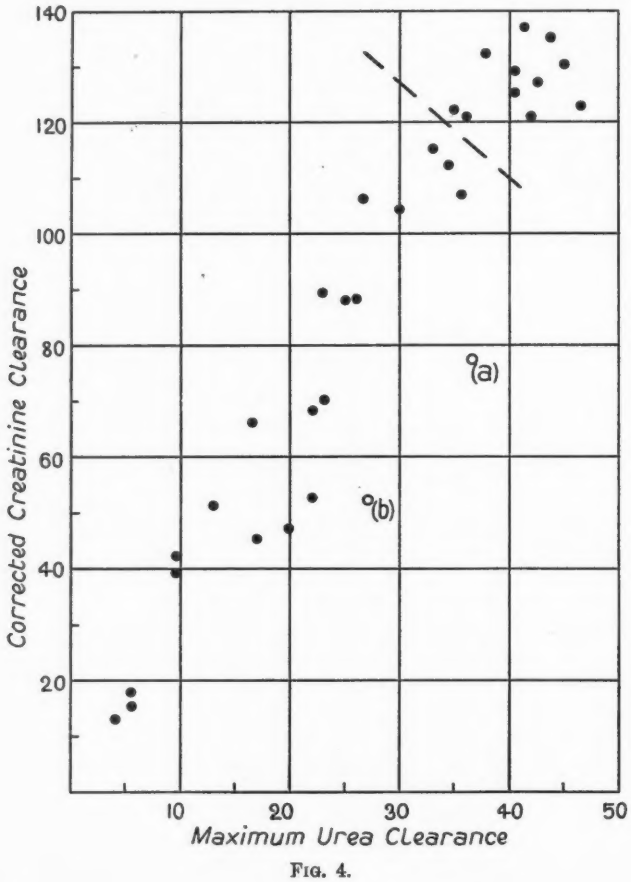

FIG. 4.

It would appear, then, that the impairment of urea excretion is paralleled by the impairment of creatinine excretion as judged by the 'corrected clearance'.

From the relatively small number of observations so far made, no clear evidence has been obtained of any dissociation of the effects of the renal lesion on the excretion of urea and creatinine. The slight concavity of the curve towards the right might perhaps be taken as tending to show that, at least in the early stages, the ability to excrete urea falls rather more rapidly than the

ability to excrete creatinine. Evidence suggesting such a possibility is contained in the observations of Van Slyke and his associates (42), that whereas blood urea concentration begins to rise above normal limits when the urea clearance falls to below 40 per cent. of its normal value, plasma creatinine does not exceed normal levels until the urea clearance has fallen below 30 per cent. of the original figure. This may, however, be due to differences in the rate of production of the two substances in the nephritic subject.

The difference in degree of impairment of excretory power for the two substances can only be small, and by no means so marked as the observations of Myers, Fine, and Lough (43), on the 'staircase effect' in the retention of uric acid, urea, and creatinine have led us to suppose. Nor do these results bear out the views of Fonteyne and Ingelbrecht (14) and of Cantinieaux (15) that in nephritis there is unequal diminution in urea and creatinine excreting powers.

There can be little doubt that, just as a seriously impaired urea excreting power may coexist with a normal or even subnormal blood urea, MacKay and MacKay (44), so a markedly impaired creatinine excretion may be present in a subject with normal or low plasma creatinine. A normal plasma creatinine, therefore, cannot be taken as evidence of an unimpaired ability to excrete that substance. Four cases in the present series illustrate this point. The resting creatinine levels of these were normal or low, although markedly deficient excreting power was revealed when the concentration was artificially raised.

Subject.	Resting Plasma Creatinine.	Uncorrected Creatinine Clearance.	Corrected Creatinine Clearance.	Urea Clearance.
Carthew	1·11	29·0	52·8	27·1
Longford	0·94	31·1	66·3	16·5
Antell	1·61	15·3	17·0	6·7
Ingram	1·02	60·4	68·2	21·9

It would appear justifiable, then, to draw the following conclusions:

(*a*) Creatinine excretion as measured by the maximum clearance is impaired progressively in nephritis.

(*b*) The impairment of creatinine excreting power parallels that of urea excretion, and the normal relation of the former to the latter of 3 : 1 is roughly maintained for all degrees of renal functional impairment.

(*c*) A normal plasma creatinine may exist when the creatinine excreting power is markedly deficient, and is, therefore, no indication of unimpaired creatinine excreting ability.

As remarked in the introduction to this paper, it is not intended to recommend the use of creatinine clearances as an index of renal failure for routine use on clinical material. Although it is the opinion of the writer that creatinine clearances give considerably more accurate information than many renal function tests at present in use, yet it would seem that, looked at from a purely clinical standpoint they merely confirm and do not extend the findings of the urea maximum clearance determination. That they do confirm the latter is

considered by the writer to strengthen considerably the claims of the urea maximum clearance test to far more extended application as a test of renal function of the greatest value.

The fact that two entirely different methods employing respectively urea and creatinine agree in their estimate of the extent of renal inadequacy suggests strongly that the information obtained by either has a definite meaning, and is a true index of the degree of inability of the kidney to excrete substances of this type.

Summary.

1. In the normal subject under conditions which have been shown by Addis to lead to a constant ratio between blood urea concentration and the rate of urea excretion, there has been found a similar linear relation between plasma creatinine concentration and the rate of creatinine excretion in the normal human subject.

2. The ratio, $\frac{\text{mg. creatinine excreted per hour}}{\text{plasma creatinine mg. per cent.} - 0{\cdot}5}$, has been found to have a practically constant value of about 125. It is suggested that the 0·5 mg. subtracted represents inert non-creatinine chromogenic substances in plasma.

3. Some evidence has been obtained suggesting that under the same conditions a similar linear relation between plasma creatinine and creatinine excretion also holds in the nephritic subject.

4. Creatinine excreting power, as measured by the ratio given in paragraph 2 above, has been found to be progressively impaired in nephritis.

5. Creatinine is excreted three times as readily as urea in the normal subject.

6. In the nephritic subject the impairment of creatinine excretion approximately parallels that of urea excretion. The normal ratio between the two of 3 to 1 being roughly maintained for all degrees of renal damage.

The author wishes to express his thanks to Professor Peters for many helpful suggestions, to other workers in the Department of Biochemistry for their help in taking blood samples, to the Honorary Staff of the Radcliffe Infirmary for their kindness in granting him access to their cases and to the Nursing Staff for their co-operation in the work on nephritic subjects.

The work has been done under the tenure of a Beit Memorial Fellowship.

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INTRACRANIAL TUMOURS[1]

A CRITICAL REVIEW

By F. M. R. WALSHE

I. Introduction.

So extensive a literature has grown up round the subject of intracranial tumours within the past twenty years, and so many and important additions to our knowledge of them have been made within this period, that a comprehensive review of the subject is not easily possible within the limits of this article; indeed the attempt to deal evenly with all its aspects could end in no more than a bald catalogue of new facts and fresh hypotheses.

A somewhat arbitrary selection of material and of emphasis has thus been necessary, and has been made. As a consequence certain important aspects of the subject have been somewhat summarily dealt with, while others may seem to have obtained undue consideration. It is clear, however, that any adequate consideration of intracranial tumours must from time to time trench upon other problems of neuropathology and thus involve references to questions that do not directly concern the subject under discussion.

Thus, the histogenesis of the normal interstitial cells of the nervous system has been briefly described as a necessary preliminary to a consideration of the glioma group of tumours, but this account serves another purpose in summarizing recent work upon the nature of the glia, and also draws attention to some observations that are full of significance from the point of view of general pathology; namely, the relationship of the microglia to the reticulo-endothelial system of cells. In this matter, therefore, and in one or two others, the writer may seem to have interpreted his subject somewhat widely.

On the other hand, the familiar localizing symptom-complexes associated with tumours in certain situations have not been fully described, attention being specially directed to those syndromes that more recent work has served to differentiate; such, for example, as those of tumours in the pituitary region, of metastatic carcinoma, and of the different types of glioma.

Again, there are many aspects of the subject of which there is no general summary available for the non-neurological reader that have been given separate chapters; such as the significance of generalized epileptiform fits as the initial manifestation of tumour, false localizing signs, radiological appearances in the skull, and the relationship of head injury to tumour formation.

[1] Received May 11, 1931.

An exhaustive account of methods of surgical treatment has not been attempted.

A brief reference to the bibliography may be opportune. Lengthy as this is, it includes but a fraction of the papers that have been devoted to this subject during the present century, but even so it will be apparent from the number of papers cited that intracranial tumours must be very common, far more common indeed than is generally appreciated.

In their recent book (7) on the classification of the gliomata, Bailey and Cushing make the bold statement that 'of all the organs of the body, with the possible exception of the uterus, the brain appears to be the most frequent seat of neoplastic disorders'.

That in 1928, Cushing was able to publish statistics of over 1,500 verified intracranial tumours that had come under his personal observation, indicates the wide experience from which he speaks, though possibly it suggests also that this experience may have been too highly specialized for the statement cited above to carry complete conviction.

It is difficult to provide figures that will give an accurate impression of the incidence of intracranial tumour, and will remain so until diagnostic skill in respect of this condition reaches the same general level as obtains with other diseases.

Nevertheless, Cushing's statement is of importance in that it draws attention to what will probably not be disputed, namely, that the brain ranks with the breast and the uterus among the commonest seats of new growth formation in the body. The numerical relation of tumours to other organic diseases of the nervous system may be gauged from the following figures taken from the Annual Report of the National Hospital, Queen Square, for the year 1928. During that year 1,309 patients were admitted to the hospital. The classified list of their diseases shows that intracranial tumours head the list with 163 cases, disseminated sclerosis follows with 132 cases, while neurosyphilis in all its forms comes but third with 113 cases. While the admissions to such a special hospital probably give no accurate idea of the incidence of cerebral vascular disease, or of such an ambulant malady as epilepsy, it seems reasonable to suggest that intracranial tumour must be included amongst the three commonest affections of the nervous system.

II. The Classification of Intracranial Tumours.

The pathological classification of tumours has become of more than academic importance. Formerly, the clinician was almost wholly concerned, firstly with the recognition of the presence of a tumour within the skull, and secondly with its localization. A pathological differentiation was rarely possible and was still more rarely attempted. Owing to the intensive studies of the past twenty years, and not least to the fruitful labours of Cushing and his co-workers, it is now in many instances possible to infer on clinical grounds the

pathological nature of a given tumour, and to determine from this its probable future behaviour and the prospects it offers of successful surgical intervention. The chief varieties of intracranial tumour are given below, with estimates of their relative frequency taken from the records of the National Hospital for the twelve years ending 1930 inclusive, and also from the list published by Cushing and Bailey (38) in 1928.

	National Hospital (Total: 642 cases).	Cushing and Bailey (Total: 1,500 cases).
	%	%
Glioma	40·5	41·5
Meningioma	13·5	12·2
Auditory nerve tumour	11·5	8·5
Hypophyseal duct tumour	8·5	6·0
Sarcoma	7·7	—
Secondary carcinoma	6·4	4·0
Pituitary adenoma	4·6	19·2
Tuberculoma } Granuloma }	2·6	2·8
Blood-vessel tumour	1·4	1·9
Choroid plexus tumour	—	—
Cholesteatoma	—	—

Since the basis of classification in each case is not always the same, a complete comparison is not possible. To Dr. Greenfield, Pathologist to the Hospital, the writer is indebted for the figures from the National Hospital.

As will later be seen, the term 'glioma' includes a wide range of tumours; alike in that they all arise from interstitial cells, but possessing pathological characteristics and clinical peculiarities of their own, as well as favourite sites of incidence.

(a) *The Glioma Group of Tumours. The Histogenesis of the Interstitial Cells of the Nervous System.*

A brief account of the component elements of the nervous system is an essential preliminary to a description of the genesis and nature of the tumours which arise within its substance.

The medullary tube from which the vertebrate nervous system arises consists of a single layer of columnar cells, the medullary epithelium, from which by growth and differentiation develop cells of three types; *neuroblasts*, the precursors of the neurone; *primitive spongioblasts*, from which probably arise two elements in the interstitial tissue—namely, astrocytes and oligodendroglia; and indifferent cells, or *medulloblasts*, the destiny of which seems less fixed and which may give rise to either of the two interstitial elements named above.

Of the variations in form and of the migrations of the developing neuroblast it is not now necessary to speak, since this cell is not that from which the glioma arises.

The fate of the primitive spongioblasts is determined by their relations to the medullary canal and to the external limiting membrane of the medullary

tube. Those that remain attached to the canal develop into ependymal cells, while those that retain an attachment to the surface of the tube become subpial glia cells. Another group which wanders into the substance of the developing medullary tube passes through various stages of differentiation—bipolar and unipolar spongioblasts—each cell developing a process attaching it to the wall of a capillary and thus becoming an *astroblast*. The further evolution of the astroblast occurs at about full term in the human foetus and consists in the radiation of fine processes from the cell body and in the enlargement of the vascular attachment into a 'sucker foot' on the capillary wall. It is this vascular foot that distinguishes this element, the *astrocyte*, from other interstitial cells. From astroblasts lying in the grey matter of the cortex and basal ganglia develop *protoplasmic astrocytes*, while those lying in the white matter become *fibrillary astrocytes*, so called because fibrils form in the cell processes and attach the astrocytes to the capillary wall and to adjacent nerve-cell bodies.

At full term, also, large numbers of migratory spongioblasts leave the region of the medullary canal, and by rapid amitotic division develop into mature cells of smaller size than the astrocytes, lacking a vascular attachment and possessing but a few fine processes. To this group of cells Hortega has given the name of *oligodendroglia*. They are the most numerous cells in the nervous system after the nerve-cells. They predominate in the white matter, where they lie in rows between the nerve-fibres (interfascicular glia), but they are also present in grey matter, where they form satellite cells, lying against nerve-cells and embracing them with their processes (51, 123, 127, 129, 130). This cell type is represented in the peripheral nervous system by the subcapsular cells of the spinal root ganglia and by the cells of the sheath of Schwann. Hortega believes that they are concerned in the formation and maintenance of myelin.

Hortega has also differentiated a third interstitial element to which he gives the name of *microglia* (124, 125, 127, 130). These small cells have numerous fine branching expansions, but no vascular attachments. They predominate in the grey matter and are largely satellite cells, their processes embracing the neurone cell bodies. Unlike the astrocytes and the oligodendroglia, microglia does not develop from ectoderm, but is mesodermal in origin. Its cells appear beneath the pia in the brain of the full-term foetus and rapidly invade the grey matter.

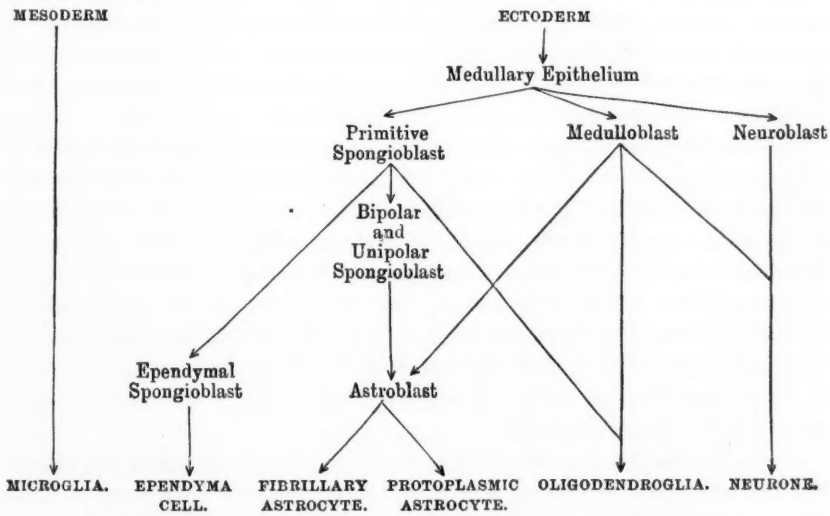
Other mesodermal elements, though not strictly part of the structure of the brain, enter into its supporting skeleton, namely, vascular and pial elements. Vessels penetrate the brain and ramify therein like the branches of a tree, each vessel carrying a pial sheath. The neuroglial astrocytes connect the vessels and the nerve-cells in the manner described. As Penfield (125) expresses it, 'The octopus-like astrocytes hold the manifold structures of the nervous system within their tentacles, and are attached to pia and vascular tree by special expansions'. To this complex skeleton Penfield gives the name of the *vaso-*

astral framework. While the functions of the astrocytes thus appear to be mainly architectural, we have seen that there is reason to suppose that oligodendroglia has a specific nutritive function in respect of myelin. The microglia also has a specialized function, as may be seen from its reactions to tumour formation, injury, and disease.

The investigations of Hortega and of Penfield already cited have shown that microglia forms the phagocytic element in the brain, and is the source of the large mobile macrophages of the central nervous system. In response to destructive lesions and tumour formation, microglia cells multiply, enlarge rapidly, lose their expansions, and become amoeboid phagocytes. In this form, long ere their origin was suspected, they have been known by a great variety of names. They are the 'Gitterzellen', 'Abräumzellen', 'Stäbchenzellen', 'compound granular corpuscles', 'scavenger cells', or 'amoeboid wandering cells' of the pathologists. It has been suggested that microglia represents within the nervous system the reticulo-endothelial cell system of the body. Not only does its reaction to disease and injury accord with this view, but so also does its reaction on vital staining, as Carmichael and Wells (*Brain*, 1930, 53, 1) and Russell (135) have recently shown.

The inclusion of a mesodermal tissue within the strictly insulated ectodermal central nervous system is of itself a matter of considerable interest, and its possible identity with the reticulo-endothelial system opens up pathological problems of considerable importance which have yet to be formulated and worked out.

The foregoing summary may be simply embodied in the two following schemes the first in terms of structure, the second in terms of function.



(1) Histogenesis of Nervous System. (Modified from Bailey and Cushing.)

VASO-ASTRAL FRAMEWORK	Blood-vessel. Pial Sheath. Astrocyte.
NUTRITIVE ELEMENT	Oligodendroglia.
RECTICULO-ENDOTHELIAL ELEMENT	Microglia.
PARENCHYMATOUS ELEMENT	Neurone.

(2) Functional Differentiation of Interstitial Elements.

With the minute characters of these various interstitial cells, as these are revealed by specific histological methods, by which they have been identified, we are not now concerned. Full details may be found in the various papers of Hortega and Penfield on this subject, but the foregoing sketch is necessary to an understanding of the various views now advanced as to the cellular origin of the diverse tumours known as gliomata, and these we may now proceed to consider.

(b) *Classification of Gliomata. (Clinical Correlation).*

By definition a glioma is a neoplasm arising from the interstitial tissue of the nervous system, and we should therefore exclude from present consideration tumours derived from parenchymatous elements; namely, the neuroblastoma and the ganglioneuroma, both of which are indeed rare tumours. Nevertheless, it is convenient to deal with them under this heading, and it has to be remembered that in various types of glioma, neuroblasts are found.

From what has been said of the composition of the interstitial tissue of the nervous system, it will be seen that there are three elements from which tumours might arise. Actually, tumours of the microglia are not known to occur, while oligodendroglioma appears to be rare. Most gliomata arise, therefore, from embryonal or adult types of glial cell of which the astrocyte is the mature representative.

It has long been known that the term glioma included tumours of widely differing macroscopic and microscopic appearances, and of varying malignancy and rates of growth. In 1913 Tooth (151) made an attempt to analyse this heterogenous group. Since this date various classifications have been made, those of Bailey and Cushing (7, 10), Carmichael (20), and Courville (23) being the most recent. A large terminology has grown up on the process and is rendered difficult of comprehension by the constant change of opinion, and by the facility with which each observer coins his own terms and rejects those of his predecessors. It is scarcely necessary to add that, in this matter, change is not invariably improvement.

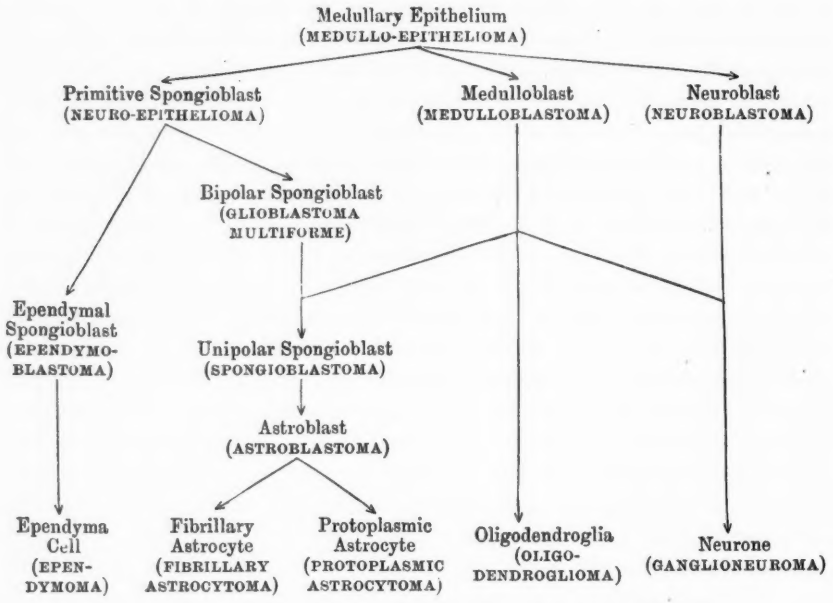
Tooth's analysis was avowedly a simple one, yet it contained the pith of the matter as far as clinical application is concerned. Examining sections from over 100 gliomas, Tooth found 'a bewildering variety of pathological appearances. . . . The same tumour may present, sometimes within the compass

of an ordinary section, grades of change of great variety, so that at one end of the section we are looking at an apparently innocent growth, and at the other a richly cellular mass, more like a malignant sarcoma, or in other places an area of necrosis'. At one extreme he found the appearance of a simple glial overgrowth: a number of small glia cells with branching processes and the appearance of a loose-meshed glia reticulum. Numerous apparently free glia nuclei were also present and a scanty supply of thin-walled vessels. Tumours of such structure gave a long history and, sometimes, a remarkable freedom from recurrence after operative extirpation. In what he regarded as a more malignant form, the glia cells were larger and more numerous and the nuclei lay in 'annular formation'. Many cells were multinucleated, the glia reticulum was very little in evidence, numerous vessels were present showing considerable intimal proliferation, and finally, vascular occlusion, thrombosis, and necrosis were seen. These phenomena he took for evidence of increased malignancy and rapidity of growth, Clinically, such tumours ran a rapid course and recurred rapidly after operation. He also observed that the partial removal of a relatively innocent variety of glioma might be followed by the changes above enumerated; that is, by the development of increased malignancy. We may sum up these observations by saying that the more the minute structure of a glioma departs from the appearances of normal glia, the more rapidly does the tumour grow and recur after operative interference. The richly cellular glioma with large multinucleated cells in annular formation is the most malignant. Finally, a single tumour may contain within itself all the cell forms and formations observed throughout the series.

In 1924 Roussy, Lhermitte, and Cornil (133) classified the gliomata as follows: (1) 'Gliome astrocytaire', and (2) 'Glioma cellulaire ou afibrillaire'. The former corresponds to Tooth's 'innocent type', and the latter to his cellular malignant type. They also named, but did not further describe, a 'Glioblastome', a 'Spongioblastome', and an 'Ependymogliome'. The last named arises from and tends to reproduce cells of the ependymal type.

Therefore, beyond lending it the precision of a nomenclature, this classification added little to Tooth's analysis.

More recently upon the basis of the Cohnheim and Ribbert hypotheses of tumour formation, Bailey and Cushing (7, 10) have evolved a far more minute subdivision of the gliomata. Applying to the extensive material at their disposal the most modern histological methods, they believe that they have found tumours that represent every developmental stage in the life history of the interstitial ectodermal cell. Their views are most easily seen from the following table in which each tumour type is placed next its parent-cell type. Although tumours derived from the neuroblast are not gliomata, the authors conveniently include them in their scheme.



Histogenesis of the Gliomata. (Modified from Bailey and Cushing.)

The Cohnheim-Ribbert hypothesis having been found inadequate as a generalization of the phenomena of new-growth formation, it is surprising that Bailey and Cushing should have stretched their admirable and exhaustive histological observations upon the procrustean bed of an abandoned theory, more especially as they are clearly aware of the difficulties inherent in doing so. While it is possible that the medulloblastoma, a tumour composed wholly of undifferentiated cells and arising in a situation where heterotopic cell formations are known to be common, namely, in the roof of the fourth ventricle, may fit into such a scheme, the tumours composed of derivatives of the glioblast (spongioblast) group present a more difficult problem. Tooth, as well as Roussy, Lhermitte, and Cornil have stressed the wide variation of cell form that may be found within the compass of a single tumour, and Tooth has pointed out the reversion to more primitive cell forms that a slowly growing glioma may show after operative interference. Indeed, the occurrence of metaplasia is a commonplace in respect of all tumours. In their book Bailey and Cushing give various examples of all these phenomena. Thus, they state (p. 98): 'It is possible that the glioblastoma multiforme may arise from protoplasmic astrocytes, for, as will be emphasized, there are several tumours in our series—tumours partially extirpated at successive sessions—which were obviously protoplasmic astrocytes when first encountered, whereas later on they had assumed the characteristics of a typical glioblastoma multiforme with numerous mitoses. In each case a de-differentiation seems to have occurred with a corresponding increase in the

rapidity of growth.' Roussy's criticism (134) may therefore be considered to express the verdict that must be passed upon the notion underlying this classification. He says that it is not demonstrated that tumours composed of cells having the appearances of incompletely undifferentiated embryonic cells really derive from cells in a state of arrested development. Metaplasia is the rule in tumours, and undifferentiated and de-differentiated cells cannot be distinguished. We cannot tell from which direction a given cell has approached the state in which we find it in a given tumour. He, therefore, requires a classification based upon morphological factors and carrying no debatable theoretical implications. Nevertheless, Bailey and Cushing's work has stimulated investigation, and fresh classification of the gliomata continue to be published, consisting essentially of simplifications and modifications of these authors' scheme. Thus, Courville (23) divides gliomata into two main groups; those composed of cells of embryonic character, and those with cells of adult character. Courville confirms Tooth's evaluation of the growth rate and relative benignity of the latter group, and its occasional reversion to a more undifferentiated type.

Carmichael (20) has attempted a simplification of Bailey and Cushing's classification upon a purely morphological basis, and he recognized the following main varieties of the glioma.

Astrocytoma fibrillare. To the naked eye this is a white infiltrating tumour, a true diffuse tumour without visible margins. Like the protoplasmic astrocytoma, which he does not separately group, it may contain a large cystic cavity. Microscopically, it has the appearance of an area of abnormally abundant astrocytes with a dense fibril network, every cell possessing one or more vascular processes. Other cell forms are absent.

Astroblastoma. Also a firm, pale tumour with ill-defined margins. Cyst formation is infrequent. Microscopically, it is not always richly cellular. Its cells are large and devoid of fibrils, but possess vascular processes. Astrocytes and glioblasts also occur within the tumour. It is a more vascular tumour than the astrocytoma, and small haemorrhages and areas of degeneration are to be found (Bailey (11)).

Glioblastoma (multiforme and unipolare). Macroscopically, these two tumours are indistinguishable. They are reddish, fleshy masses with a well-defined margin. They are highly vascular. Haemorrhages and small cyst formation are common, and regions of degeneration and necrosis at the centre of the mass are frequent (Globus and Strauss (73)). Microscopically, glioblastoma multiforme consists of relatively undifferentiated round or oval cells arranged on no special plan. Large multinucleated cells are to be seen. Mitotic figures are abundant at the margins, while compound granular corpuscles are seen throughout. Glioblastoma unipolare is less vascular and less prone to degenerative changes. Its cells are of many forms, many like those of glioblastoma multiforme, but a few astroblasts occur. Indeed, there is no precise qualitative difference between the two.

Medulloblastoma, the fourth ventricle tumour of childhood, is vascular

and composed of masses of rounded undifferentiated cells of moderate size. Rosette formation is sometimes seen. This tumour tends to spread throughout the pia-arachnoid, giving rise to the so-called 'sarcomatosis' of the meninges (Nonne (116), Firor and Ford (63)).

While Courville groups all gliomata into embryonal and adult types, Carmichael groups them into corresponding glioblastic and astroblastic types, according to the degree of differentiation of the component cells. The possession of vascular processes is Carmichael's standard of differentiation between the two. Thus, the glioblastoma and the medulloblastoma are 'glioblastic', and the astroblastoma and the astrocytoma are the 'astroblastic' tumours.

In addition to Carmichael's four types we must accept the oligodendroglioma, the ependyoma, and the pinealoma.

Oligodendroglioma is a rare form of tumour. Bailey and Bucey (9) have described thirteen cases. They find it to be a slowly growing tumour of the cerebral hemispheres of adults. It has a uniform cellular structure, the component cells possessing staining reactions and appearances which the authors believe to justify a belief in their origin from oligodendroglia.

Ependymoma. The ependymal epithelium derives from primitive spongioblasts that remain attached to the internal limiting membrane of the medullary canal. The glioma arising from these cells is a firm tumour commonly arising from the roof of the fourth ventricle, from the walls of the other ventricles, or from the spinal canal (Bailey (5), Fincher and Coon (62), Hirsch and Elliott (88)).

Pinealoma. Pineal cells arise from the medullary epithelium and consist in parenchymal and glial elements. The pineal tumour is composed of nests of cells in an interstitial reticulum, the cells showing varying degrees of de-differentiation (7, 10, 91, 92).

Penfield (128) accepts the types described by Bailey and Cushing, but proposes a simpler classification as follows:

(1) Neuro-epithelioma; (2) Glioblastoma multiforme; (3) Medulloblastoma; (4) Oligodendroglioma; (5) Polar spongioblastoma; (6) Astroblastoma; (7) Astrocytoma; and (8) Ependymoma.

It is not to be expected that any of the foregoing classifications will be final, and it is probable that when a generally agreed basis of classification is reached, it will lie somewhere between Tooth's generalization and Bailey and Cushing's complex and somewhat arbitrary scheme.

Tissue reaction to the presence of a glioma. The role of the microglia in phagocytosis has been mentioned above. In this connexion Penfield (124) has made the interesting observation that in the presence of a glioma, just as in that of a destructive lesion, there is an active microglial reaction. The large macrophages invade the tumour and are engaged in dendrophagocytosis, carrying the products of degeneration to the vessels where they are deposited in the adventitial sheaths in the regions immediately surrounding the tumour. The astrocytes and oligodendroglia appear to take no part in this process.

Clinical correlation. Certain generalizations are possible as to the age incidence, localization, and clinical course of the various tumours thus histologically differentiated.

The glioblastoma is a tumour of the cerebral hemisphere, including the corpus callosum. It occurs in middle life and is the most rapidly growing variety. It recurs rapidly after operation, and does not respond to radiotherapy. Frequently after partial extirpation, death occurs within a few days from swelling of the brain. Glioblastoma constitutes approximately 30 per cent. of all gliomata (Globus and Strauss (73), Bailey and Cushing (7, 10), Penfield (128)).

The astrocytoma occurs in the cerebrum and cerebellum. In the former situation it is most frequent in the third and fourth decades of life, but its maximal incidence in the cerebellum appears to be between the ages of 5 and 15 (Cushing (37)). In the latter situation it is commonly cystic; a large cyst containing xanthochromic fluid carries a tumour nodule in its wall. It arises in the mid-line, but the cyst may spread into one of the lateral lobes more than into the other. The astrocytoma is a slow-growing, relatively benign tumour, and when in the cystic variety the mural nodule is removed the expectation of life is very good. The medulloblastoma and the cystic astrocytoma comprise the majority of cerebellar tumours in childhood.

The medulloblastoma is almost exclusively a cerebellar tumour of the first decade of life. It approximates to the glioblastoma in rapidity of growth and in malignancy, and it tends to invade the pia-arachnoid (Cushing (6, 37)).

The ependymoma is also a tumour of childhood, and is frequently cerebellar in incidence. It is more slowly growing than the medulloblastoma, and may be clinically latent for a period of years. When in the cerebral hemispheres and accessible, the prognosis after extirpation is fairly good.

The rare *oligodendroglioma* is the most slowly growing of all, in so far as the limited available experience of this tumour goes, and in one of Bailey's reported cases generalized epileptiform fits preceded the appearance of focal and pressure signs by seventeen years. In a few cases long periods of operative survival are recorded. It appears to be a cerebral tumour of adults.

(c) *Meningioma.*

Arising in the mesodermal meninges that insulate the ectodermal nervous system from surrounding tissues are two varieties of intacranial tumour; the dural endothelioma, or meningioma, and the auditory nerve tumour. Together these constitute about 20 per cent. of the tumours in Cushing's series (38), a figure which accords approximately with Tooth's (151) earlier finding.

The histogenesis of these tumours is not yet a matter of general agreement, and the reader of the literature on the subject is left with the impression that an exclusive pre-occupation with the nervous system has resulted in a tendency to create an *ad hoc* pathology for them that takes little account of the origin and potentialities of the connective tissue cell (Mallory (110), Penfield (126)).

The origin of the dural endothelioma. Although the naked-eye attachment of this tumour is to the dura, it is generally agreed that it arises from the proliferation of arachnoid cells where these impinge upon the dura in the walls of the dural sinuses. The arachnoid villus (32, 158), through which the cerebrospinal fluid drains back into the venous system, consists of a connective tissue stroma, upon the apex of which is a cluster of arachnoid mesothelial cells. The villus worms its way through the fibrous dural wall of the sinus, and its cellular cap lies free in the lumen. On section of the dura, clumps of such cells may be seen lying in the interstices of the dura. The dural endothelioma is nothing but a mass of such cells embedded in a stroma of dural origin, and supplied with blood by dural arterioles. It is, in short, a kind of hypertrophied Pacchionian granulation. Seen under the microscope a single field of an arachnoid villus and a field of a dural endothelioma are indistinguishable. Mallory (110) and following him Penfield (126) believe that the type of cell of the endothelioma is the fibroblast. But the differentiation of connective tissue cells by the method of vital staining appears to show that the mesothelia arachnoid cell behaves like the fixed histiocytes, and such changes as it may undergo is rather in the direction of the macrophage than the fibroblast. There is probably a wider range of variation in the naked-eye and microscopic appearances, and in the behaviour of the tumours of this group, than a study of the literature indicates. Thus, Cushing and Bailey (38) refer to the occasional occurrence of a meningioma which in its gross and minute appearance bears many resemblances to the haemangioblastomata to be considered subsequently.

The histogenesis of the meningioma may therefore be regarded as an incompletely elucidated problem, and in the meantime Cushing's non-committal term 'meningioma' is probably the most apt. While the meningioma is commonly spoken of as a benign tumour, it has to be remembered that rare examples of metastasis are on record (Purves Stewart (132), Towne (152)).

A characteristic of this tumour is its tendency to invade the overlying bone, leading to the formation of a rounded or nodular boss on the skull. Cushing (32) reports that such bony invasion occurs in some 20 per cent. of cases. Penfield (121, 126), Phemister (131), and Taylor (150) have studied these bony lesions. New bone formation and rarefaction go on side by side. The venous channels in the bone are dilated and contain tumour cells. Penfield, while stating that the bony enlargement is not a hyperostosis, believes that it is not comparable with the invasion of bone by a malignant growth, but he gives no grounds for this view, and Taylor has shown that the meningioma behaves to the skull just as a periosteal sarcoma does to the long bone of a limb. In the two cases the radiographic and the histological pictures are the same.

Localization of the meningiomata. From what has been said of their origin, it follows that these tumours must develop in certain sites of election, namely, in the neighbourhood of dural sinuses. Cushing has classified them on this basis as follows: parasagittal meningioma, meningioma of the falx, of the

sinus transversus and sigmoideus, of the convexity, of the Sylvian cleft, of the sphenoidal ridge, of the olfactory groove of the ethmoid, of the cranial nerve foramina, and suprasellar. Of these, the parasagittal and the convexity group are the most numerous. Infratentorial meningioma is relatively uncommon. On the whole, this tumour most commonly lies in the anterior half of the skull, and the frontal lobes are the portions of the brain most often compressed by them (Cushing (32), Holmes and Sargent (75)).

Being of mesodermal origin, it is not surprising that the meningioma does not invade the brain, but pushes brain and pia-arachnoid before it. It is usually an irregularly rounded tumour, but may be a flat mass which spreads circumferentially. The latter is especially the case when it arises on the floor of the skull, where it spreads like a gradual lava flow, involving the various cranial nerves in slow succession.

Clinical characteristics. The meningioma is a very slowly growing tumour, and since it is most commonly situated where it does not give rise to hydrocephalus, the onset of symptoms may be long delayed, and even then indeterminate in character. It is not surprising that, as Cushing observes, frontally placed tumours of this class should sometimes be accidental post-mortem discoveries in the inmates of asylums. The slow development of mental symptoms, and the delayed onset of pressure signs, lead to a diagnosis of mental disorder, which once made is never revised. Here, as with the slow growing gliomata, generalized epileptiform convulsions, recurring at irregular intervals, may for years be the sole manifestation of tumour, and even when the age of the patient awakens the suspicions of the observer, repeated clinical and radiographical investigations may prove negative until the final and rapid development of signs of intracranial tension. In other words, a diagnosis of intracranial tumour, quite apart from any question of localization, may prove a matter of considerable difficulty until the terminal phase of the illness is reached.

(d) *Auditory Nerve Tumour.*

This tumour arises from the endoneurium of the nerve at its distal part, where it lies in the internal auditory meatus. Its growth in this situation often leads to absorption of the bone and to a dilatation of the meatus that may be visible in a radiogram. It lies within an arachnoid capsule, surrounded by a collection of cerebrospinal fluid. In the course of its growth, the tumour surrounds and compresses the eighth nerve, while the other nerves which traverse the lateral part of the posterior fossa, namely the fifth, seventh, ninth, tenth, eleventh, and twelfth, are stretched round its circumference. In this process of embracing the tumour these nerves undergo considerable elongation, though the disorders of function resulting therefrom are notably slight in most instances. In the course of time the cerebellum and pons are compressed, deformed, and displaced, the aqueduct of Sylvius becomes blocked in consequence and hydrocephalus is produced (Cushing (29)).

Histogenesis. There is some difference of view as to the origin of this tumour. It may be solitary or occur as part of a generalized neurofibromatosis (von Recklinghausen's disease), and in the latter case it may be bilateral. Mallory (110) and Penfield (126) believe that the solitary eighth nerve tumour is a fibroblastoma strictly comparable with the meningioma, while the eighth nerve tumour of a neurofibromatosis is a true neurofibroma, the connective tissue of which is part of a general connective tissue reaction. Actually, microscopic examination may quite fail to differentiate to which group a given eighth nerve tumour may belong, while in no case does such a tumour resemble the meningioma. This histological problem may therefore be considered as not yet satisfactorily resolved, and it probably requires for its solution the same broad pathological outlook that has been postulated as desirable in the case of the meningioma.

Clinically its symptom-complex has a remarkable constancy both in its evolution and in its components, and in virtue of the former this tumour can generally be differentiated clinically from other tumours in the same situation in the skull (Horrax and Buckley (93)). The initial symptoms are referable to the auditory nerve and consist of gradually increasing deafness with tinnitus. Later, paraesthesiae on the same side of the face and loss of the corneal reflex indicate interference with the fifth nerve, while a slight weakness of facial movement indicates involvement of the seventh. In rare cases twitching of the facial muscles occurs (Stewart and Holmes (76), Cushing (29)). Symptoms of cerebellar disorder then follow, and are accompanied by the rise of intracranial tension due to hydrocephalus. Headache, vomiting, and vertigo, with papilloedema are generally present by the time that the patient comes under observation. At this time, also, there is complete deafness and loss of the caloric labyrinthine reactions on the affected side.

(e) *Tumours of the Pituitary Region.*

These are most readily understood in the light of the development and relations of the pituitary body. When by the formation of the sella turcica the distal portion of the cranio-pharyngeal pouch (Rathke's pouch) is cut off from that part of it which united it to the stomodaeum, the cells of the separated portion proliferate to form the anterior lobe of the pituitary body, those of the anterior wall forming the anterior lobe, those of the posterior wall the intermediate part. Between them a cleft represents the original lumen of the craniopharyngeal duct. The tip of the down-growing infundibular process from the floor of the third ventricle enlarges to form the posterior lobe, which joining the epithelial portion forms with it the complete pituitary body. The fully developed organ thus consists of (i) a large *pars anterior*, which forms two-thirds of the entire structure; (ii) a small *pars intermedia*, which forms an epithelial covering to the posterior lobe; and (iii) a *pars tuberalis*, which is a thin collar-like glandular structure encircling the pituitary stalk at its origin

from the tuber cinereum. These three constitute the epithelial, glandular portion of the pituitary; (iv) the *pars nervosa*, or posterior lobe, lies behind the anterior lobe and consists of neuroglia-like tissue with a few nerve-fibres. As will be later seen, the pituitary complex stands in close physiological relationship to the tuber cinereum and hypothalamic region. In addition, there remain in many instances small collections of cells which are remnants of the original cranio-pharyngeal duct. They lie in two chief collections on the anterior aspect of the pituitary stalk, one at its lower end where it joins the pituitary body, the other at its place of origin from the brain. Finally, the dura mater roofs over the sella, and the sellar diaphragm contains the elements from which a meningioma may arise, namely, a dural venous sinus and arachnoid villi.

The various tumours in this region may be classified as follows:

Sellar	Pituitary body	*Adenoma.* Chromophobe. Chromophile. Mixed cell. Adenocarcinoma. Metastatic tumour.
Suprasellar	Hypophyseal duct	Papillary cyst. *Adamantinoma.* Carcinoma.
	Non-pituitary	*Meningioma of sellar diaphragm.* Primary glioma of optic chiasma.

Of these, the pituitary adenoma, the adamantinoma, and the suprasellar meningioma are the commonest. The last two members of the group are pathologically non-related to tumours of the pituitary, but may usefully find a place in the table on topographical grounds, since their clinical expression may closely resemble that of tumours arising in the pituitary body or its stalk. While the neighbourhood signs and symptoms follow the same general lines in the case of these various lesions, the glandular disorders which ensue from them show wider differences, the elucidation of which has been the work of many observers, and here as elsewhere in the general subject under discussion the contribution of Cushing and his co-workers has been an outstanding one (27, 35, 36, 39, 40, 41, 42, 56).

Pituitary adenoma. It will be recalled that upon the basis of form and staining reactions, cells of three main types have been differentiated in the pars anterior of the pituitary body, namely, (i) chromophobe, or neutrophile cells; (ii) acidophile cells containing granules that take an eosin stain, and a small number of (iii) basophile cells. Adenoma may arise from either of the two first-named varieties, and less commonly a mixed-cell adenoma containing both may be seen. Of these, by far the commonest is the *chromophobe adenoma.* It consists of closely packed cells, sometimes in alveolar formation, and is a slow-growing tumour of adult life. It may reach a considerable size, overflowing the sella and expanding above and beside it, so that in some instances it causes compression and deformation of the surrounding brain. It invariably

produces the clinical picture of 'hypopituitarism', to be described below. The less common *acidophile adenoma* is also a slow-growing tumour of adult life, may reach a great size, sometimes undergoes cystic degeneration, and is always associated with acromegaly (hyperpituitarism) (Cushing, *loc. cit.*, Cushing and Davidoff (39)). Dott and Bailey (56) have also recorded the occasional occurrence of the mixed-cell adenoma, and its association with a mixed picture in which elements of hypo- and of hyperpituitarism ('dyspituitarism') are to be noted.

The rare *adenocarcinoma* is a rapidly growing, metastatizing tumour.

Hypophyseal duct tumours. The origin of these tumours in cell rests of the cranio-pharyngeal duct was first pointed out by Erdheim (59), and the recent comprehensive study of Critchley and Ironside (24) have now made it possible to form a clear pathological and clinical picture of them.

Their minute structure and macroscopic appearance vary widely, but most of their features are comprehensible in the light of their cellular derivation from the epithelium of the primitive stomodaeum.

They consist of a solid epithelial tree with branching and anastomosing offshoots, lying in a glial or fibrous stroma. Commonly, greater or less extensive cyst formation, calcification, keratinization, and colloid deposition occur in them. In most of them, some part of their epithelial structure reproduces the characteristics of the embryonic enamel organ, presenting here an appearance like that of the epithelial odontomes of the jaw. Such tumours are called adamantinomata, the enamel-forming cell being known as an adamantoblast or ameloblast.

In other tumours the enamel-forming organ is not represented and the structure is that of a squamous papillary cyst (Duffy, *Ann. Surg.*, 1920, 72, 537). Very rarely a solid spindle-celled malignant tumour may occur.

To the naked eye the adamantinoma is an irregularly rounded, encapsulated mass; its situation and direction of expansion depending upon whether it arises from the lower of the two cell rests mentioned earlier, or from that which lies immediately beneath the brain at the upper end of the infundibulum. When from the former the tumour arises primarily within the sella, enlarging it in all directions, the pituitary body being compressed beneath the tumour. The roof of the sella is bulged upwards and pressure exerted upon the posterior aspect of the chiasma. When derived from the upper cell rest the tumour is primarily suprasellar and tends to expand upwards, bulging through the yielding floor of the third ventricle, the cavity of which may be wholly obliterated. The chiasma in these circumstances lies below and anterior to the tumour, the pituitary body is not so severely compressed, and the sellar deformation is minimal. In the more malignant cases the dura and also the base of the brain may be invaded. On section, such a tumour is seen to contain numerous cystic cavities of irregular outline. These are filled by fluid of a colour and consistency that vary from case to case. Cholesterin crystals may be present. The cyst walls are thick, have an irregular surface, and commonly contain calcareous areas and nodules.

The microscopic characters of the tumour have been minutely recorded by Critchley and Ironside, to whose paper the reader may be referred for further details.

Suprasellar meningioma. This tumour has hitherto been regarded as rare, but, with the greater degree of refinement in pathological diagnosis now possible on clinical grounds, it is probable that this type of suprasellar growth may be more frequently observed than in the past. In a series of eighty-five meningiomata described by Cushing in 1922, eight such cases occurred (32), and more recently Holmes and Sargent (75) have recorded ten further cases. They are rounded or dome-shaped tumours (the inferior surface being concave in the latter case), resembling the meningiomata already considered in gross structure and microscopic anatomy, and expanding in all directions above the sella, compressing the chiasma anteriorly and the floor of the third ventricle above (Cushing and Eisenhardt (40)).

Primary glioma of the optic chiasma. Martin and Cushing (111) have reported seven cases of primary glioma of this structure. The tumour is a bilaterally symmetrical enlargement of the chiasma, and may tend to spread backwards and invade the interpeduncular space. Four of their cases were in children under ten years.

(f) *Metastatic Carcinoma of the Brain* (*Carcinomatosis of the Meninges*).

The frequency of secondary carcinoma of the brain is difficult to estimate. It commonly occurs as a terminal phase in the history of viscera carcinoma, and is overshadowed by the symptoms of visceral disorder and by cachexia. Perhaps it would be more correct to say that the manifestations of secondary carcinoma of the brain are frequently of an indeterminate character, and it is easier to dismiss them from consideration by the facile invoking of a terminal toxaemia than to study them. Hence it is that most of our information on the subject is derived from the study of cases in which signs of a nervous lesion have preceded or dominated those of visceral disease, and in which—as a consequence—the patient has undergone an adequate neurological examination. Probably it is exceptional for this to happen, and it is safe to regard as an underestimate the 4 per cent. of metastatic growths recorded in Cushing's series (38), and the 3 per cent. recorded by Tooth in 1913 (151).

In 1908 Bruns (18) drew attention to the importance of the lungs, breast, and stomach as the source of primary carcinoma in cases of secondary cancer of the brain. Owing to the increase within recent years of reported cases of carcinoma of the lung, the frequency of this association of lung and brain has become more widely recognized and is an interesting parallel to the complication of bronchiectasis by cerebral abscess. Dosquet (54) found secondary carcinoma of the brain in 31 per cent. of 105 cases of primary cancer of the lung, and more recently Globus and Selinsky (74) and Ferguson and Rees (61) have put similar observations on record. We may regard the breast, lung, stomach, and prostate

as the common sites of the primary growth in secondary carcinoma of the brain.

There are usually very numerous deposits, some macroscopic and others revealed only on microscopic examination (Hassin and Singer (86), Lewis (105)). The visible deposits are rounded, sharply defined, soft, and loosely attached to the surrounding brain. They are usually of a pinkish colour. Hassin and Singer state that widespread toxic changes are visible throughout the brain in such cases, but Meyer (85) suggests that these changes may be a consequence of compression and of disturbed blood-supply, and are probably not inflammatory in nature.

Much less widely recognized and of considerable interest is the microscopic infiltration of the pia-arachnoid by cancer cells that may occur either in association with macroscopic nodules of growth in the brain, or alone. In the latter case it is probable that they escape notice, since it is not the practice of pathologists to look for this lesion, and it can be found only by direct search.

A condition of diffuse 'gliomatosis' or 'sarcomatosis' of the brain and cord is well known and is the subject of a considerable literature (Bassoe and Shields (14), Firor and Ford (63), Fried (63), Nonne (116), Spiller (145)), but the so-called 'carcinomatosis of the meninges' or 'meningitis carcinomatosa' appears to have attracted little notice, though certain writers have noted its presence in connexion with large tumour nodules (Cornwall (22), Grant (77), Morse (114), Globus and Selinsky (74) in America, and much earlier, Seifert (143), Saenger (136), Scholz (138), Stadelmann (147), Schuster (139)). Walshe (155) recorded a case of isolated carcinomatosis of the pia-arachnoid in this country, and reviewed the literature in 1923 (156).

(g) *Blood-vessel Tumours of the Brain.*

Interest has recently been aroused in these rare tumours, largely owing to the observation of Lindau (107) that a type of cerebellar cyst hitherto regarded as gliomatous contains an angiomatous nodule in its wall. In a few recorded examples this lesion has been found in association with retinal angioma, cystic disease of the pancreas and kidney, hypernephroma and angiomatosis of the liver. Though the various components of this syndrome have long been recognized, it is now spoken of by Cushing and Bailey (38) as Lindau's disease, but since more often than not the combination is incomplete and cerebellar angiomatous cysts may exist alone, there seems no reason for labelling the last-named condition by this name. It is to Cushing and Bailey (38) that we owe the most comprehensive description of true blood-vessel tumours of the brain. Their frequency may be deduced from the fact that these authors have found them in approximately 2 per cent. of their series of 1,522 intracranial tumours. They divide them into two classes: congenital *angiomatous malformations* and *haemangioblastomata*, the latter being true neoplasms arising from angioblastic elements.

The *angiomatous malformations* include telangiectases, which are of little clinical significance, and of venous and arterio-venous angiomata. The purely venous angioma consists of a more or less complex coil of veins upon the surface of the cerebral hemispheres, and in some instances going deeply in wedge-shaped formation as far as the ventricular wall. It is characterized clinically by the occurrence over a long period of years of Jacksonian fits, and frequently by the presence in the territory of the homolateral trigeminal nerve of cutaneous naevi. Sometimes, also, calcification in the walls of the constituent vessels gives a characteristic radiographic picture by which the condition may be identified (117). Signs of raised intracranial tension are not found. The arterio-venous angiomata, in addition, are associated with a cranial bruit, with unilateral or bilateral exophthalmos, and with signs of raised intracranial tension which frequently lead to a diagnosis of intracranial tumour. Decompression appears the only operative procedure of value, but there is some evidence that radiotherapy may lead to thrombosis and fibrosis of the constituent vessels.

The *haemangioblastoma*, as hitherto recorded, is an almost exclusively cerebellar lesion, and like the angiomata may give rise to symptoms at any age. Cutaneous naevi are not present, and the clinical diagnosis is one of cerebellar tumour. Commonly, it occurs without the associated lesions mentioned above, though it is possible that—attention having been directed to the occurrence of retinal angiomatosis—this lesion may be more frequently observed in future. It is a true neoplasm arising by the proliferation of angioblastic cells, and may assume a solid, a capillary, or a cavernous form according to the arrangement and mode of growth of the cells. In most cases the tumour consists of a small nodule in the wall of a large cyst which contains xanthochromic fluid. This is believed to arise by transudation from the tumour. In the past the tumour nodule has either been so small as not to attract attention, or it has been regarded as a glioma. So far, only a single unequivocal example of haemangioblastoma of the cerebrum (Barnard and Walshe (12)) has been recorded, but it is probable that attention being now directed to this class of tumour further examples will come to light, and it is premature to assert that such tumours are invariably cerebellar.

(h) *Other Varieties of Tumour.*

There remain for brief consideration a few tumours of rare occurrence not previously classified.

Cholesteatoma. This is the 'pearly tumour' of Cruveilhier, relatively common in the lateral ventricle of the horse's brain, but rare in the human subject. It is believed to arise from a foetal epithelial inclusion, in which the epidermal elements of the skin are represented. Occasionally, when deeper layers are included, hair may be found within the tumour. Such tumours are found beneath the pons, or mid-brain, extending into the cerebello-pontile angle, but may occur in the arachnoid cisterns at any part of the base of the brain.

They are subarachnoid in situation, and have a pial capsule. The inner surface of this is covered by layers of cells representing the skin layers, and the body of the tumour consists of waxy, brittle material containing kerato-hyalin and cholesterin. There are no blood-vessels within the mass. The tumour derives its name from its white, glistening, and nacreous capsule. Its relation to the cholesteatoma of the middle ear remains disputed, though there are some who regard the latter as an epithelial neoplasm that has become secondarily infected (Mackenzie (108)). Horrax (89), Bailey (4), and Critchley and Ferguson (25) have given exhaustive clinical and pathological descriptions of the cholesteoma, a tumour for which the alternative name of 'cerebral epidermoid' has been suggested.

Neuroblastoma. The tumour formerly known by this name (Greenfield (80)) is the astroblastoma of Bailey and Cushing's classification. The term is now employed for a rare neoplasm, the cells of which resemble neuroblasts. It is a circumscribed relatively benign tumour growing within the brain. Calcareous masses may be found in its substance.

Choroid papilloma. A rare papillomatous tumour developing in connexion with the choroid plexuses in the ventricles (Davis and Cushing (50)).

Tuberculoma. There are no recent studies of tuberculous tumours, but estimates of their frequency appear to differ widely. Thus, Batten (*Diseases of Children*, Garrod, Batten, and Thursfield, 1913) states that they constitute 50 per cent. of intracranial tumours in childhood, and Buzzard and Greenfield (80) regard it as among the commonest of brain tumours. On the other hand, the granulomata constitute only 3 per cent. of Cushing's series that has been cited earlier. Since it is generally agreed that tuberculomata are most commonly found in the brain-stem and cerebellum, it would be of value if some characteristic clinical differences between cerebellar gliomata, on the one hand, and cerebellar tuberculoma could be established. At present, collateral evidence of tuberculosis elsewhere in the patient has to be relied upon.

Syphiloma. Observation shows that this is probably among the rarest of intracranial tumours, and also that the presence of a positive Wassermann reaction in the blood in an individual presenting the signs of tumour is of itself not an adequate reason for concluding that the tumour is a gumma. Intracranial new growths are common and syphilis is not rare, and it is probable that this combination is more frequently seen than is a cerebral gumma. In all such cases, therefore, confirmation of the presence of active cerebral syphilis must be sought by a careful examination of the cerebrospinal fluid, for which the hopeful invocation of Ockham's razor is no substitute. Further, as Horsley used to point out, in the presence of a gumma of any dimensions, vascular lesions and general compression may so interfere with the circulation through the region of the brain involved that anti-syphilitic remedies are precluded from obtaining access to the lesion. In these circumstances decompression may be necessary to relieve this disability as well as to counteract the ordinary consequences of raised intracranial tension, just as is the case with other varieties of tumour.

III. The Aetiology of Intracranial Tumour: Trauma.

The cellular derivation of intracranial tumours has already been considered, but in the matter of their causation the same obscurity prevails as in the case of new growths elsewhere in the body, and this is not the place to dwell upon the problems of general pathology involved.

However, brief consideration may be given to a factor that is widely regarded as of occasional significance in provoking the relevant tissues of the nervous system to neoplastic activity: namely, head injury.

Trauma, like those chronic intestinal infections of which we hear so much and know so little, is one of a group of hypothetical aetiological factors that are extensively invoked in explanation of those affections of the nervous and other systems, the true causation of which is hidden from us.

Nevertheless, the widespread and unscientific employment of this and similar explanations should not deter us from a consideration of such reasonable evidence as may be available concerning a relationship between head injury and the growth of intracranial tumour. Such a relationship is necessarily extremely difficult to establish, and in comparatively few of the reported cases of the kind is the evidence sufficient to justify any definite conclusions. In his many contributions to the subject of intracranial tumour, Cushing makes numerous references to this point. Thus in connexion with pituitary tumour (27), he says that 'unquestionably traumatism plays a certain role', and again, 'the incidence of trauma in relation to intracranial tumour in general is well recognized and represents roughly about 15 per cent. of our series of some 300 cases'. Nevertheless, the five cases he cites in the book in question are not of themselves particularly convincing, and indicate merely a sequence of events that are not obviously related. But it is in connexion with the meningiomata that he provides the most conclusive evidence. He states (32), 'In so many of the cases in the series has a tumour been found at the exact situation where a stunning blow has been received on the skull years before, that this must represent something more than mere coincidence'. He suggests that a local extravasation of blood in these cases has led to an abnormal proliferation of arachnoid cell clusters that has ended in tumour formation. Elsewhere (31) he cites an important example: Twelve years previously the patient had sustained a severe blow on the vertex at the Rolandic point. This had remained tender, and in course of time a local prominence of the skull had appeared. With the development of this, focal Jacksonian fits in the foot had ensued. Seven years after the injury the thickened bone was excised and found to be infiltrated by endothelioma, but the underlying dura was not incised. The fits continued unabated, and a spastic weakness of the left leg developed, to be followed by a slowly progressive left hemiparesis. Twelve years after the original injury a large 'potato-like psammo-endothelioma' weighing 198 grm. was removed. It was attached to the longitudinal sinus wall immediately beneath the original bone defect.

In 1907 Spiller (145) had reported a similar case, and yet another has recently come under the notice of the present writer. Sixteen years previously the patient had sustained a severe blow on the skull, about an inch to the left of the mid-line and two inches behind the Rolandic fissure. For this he was trephined, but operation details are lacking.

He made a complete recovery and continued in good health until April of 1930, when he suddenly developed a complete right hemiplegia. Four weeks later he became comatose and died seven weeks after the onset of hemiplegia. To the doctor under whose care he was at the time of death, nothing was known of the previous head injury, and a diagnosis of cerebral thrombosis was made. *Post mortem* the irregularly rounded bone defect resulting from the operation of sixteen years ago was revealed in the situation already specified, and immediately beneath it was found a large meningioma, 6·5 cm. in diameter and 3·5 cm. in depth. This was attached to the wall of the longitudinal sinus, and immediately above this point of attachment the skull was thickened and abormally vascular, though no external prominence was present. Deep to the tumour was a large region of recent softening extending into the internal capsule.

In this instance the occurrence and the exact site of a local skull injury were known, and, as in Cushing's case, beneath the latter lay a meningioma. It is impossible to escape the conviction that in these two cases we are dealing with a sequence of closely related events.

In the case of a glioma a relationship of this order is much more difficult to establish (Cushing (7)), but there are some cases in the literature in which its existence seems probable. Thus, Ironside and Güttmacher (97) record the case of a man of 59, upon whose head a tree fell fracturing the skull. He returned to work in a week, but became subject to generalized epileptiform fits and was noted to be mentally dull and to be losing his memory. Headaches and drowsiness supervened. After death, some seven months following the injury, the fracture of the skull (situation not specified) was found and also a soft gelatinous tumour in the corpus callosum in its posterior third. The lateral ventricles were dilated and filled with blood-clot.

However little importance one may wish to attach to these various observations, the events and the findings in question make it impossible to maintain that there may not be a relationship of cause and effect in those cases in which an intracranial tumour develops in topographical relationship to the seat of a blow upon, or damage to, the skull.

IV. The Symptomatology of Intracranial Tumour.

We have already seen that the rates of growth of the different varieties of intracranial tumour, both those within and those outside the brain, vary widely. While in some instances the condition appears to run its course from onset to death within a year, in others there is evidence of the gradual growth of

a tumour over a long period of years. In such cases it is often only within the last few months of life that unequivocal signs of tumour may be present, and it is only in retrospect that earlier—and at the time—misunderstood symptoms assume their true significance. It is particularly in the case of those tumours which for months or years show themselves solely by the periodical occurrence of generalized fits that this slow and almost latent course is exemplified. In these circumstances it becomes obvious that the recognition of intracranial tumour may be a matter of great difficulty, and that diagnosis may be possible only in the terminal phases of its development. Opinions will vary on this point according to the individual experience of the observer. The neurologist who has to pick out the tumours from the mass of clinical material ranging from the neuroses to the acute inflammatory and vascular lesions will not hesitate to confess the obscurity that may surround the earlier stages in the growth of a tumour, while on the other hand, the surgeon who sees only those cases that have been submitted to him on clinical grounds—as suspected cases of tumour—may be inclined to regard diagnosis as a comparatively simple matter. Thus, Dott, speaking from the latter point of view (55), states that 'the diagnosis of the existence of a space-occupying lesion within the skull is usually an easy matter. Headache is the characteristic symptom.' Elsewhere he points out that headache is a symptom of raised intracranial pressure. Yet it is a commonplace that such a rise of pressure may be a long delayed and terminal phenomenon in cases of intracranial tumour, and headache accordingly a late symptom. The notion that the recognition of tumour within the skull is an easy matter is, therefore, in many instances at least, quite ill founded.

There appear to be three ways in which an intracranial tumour may manifest its presence. It may produce the signs of a slowly progressive local lesion; such, for example, as a gradually developing hemiparesis. It may give rise to raised intracranial tension and the symptoms thereof, while finally it may give rise to periodical fits indistinguishable from those of idiopathic epilepsy and occurring in an individual otherwise presenting no signs or symptoms whatever of disease.

For reasons that will be considered, it seems just to regard the last-mentioned symptom as in a class by itself.

It is in the first and last circumstances that diagnosis presents its greatest difficulties.

Further, the presence of tumour being recognized, the equally important question of its localization arises. When, as is not uncommonly the case, the signs of raised intracranial tension are the sole indications of tumour, this may present insuperable difficulties. These are not only of a negative character, but are in part positive and due to the appearance of what have been called 'false localizing signs' (Collier (21)).

Certain other generalizations may be made before proceeding to a more detailed consideration of these various factors in the symptomatology of intracranial tumours.

It is a matter of common experience that in young persons, and particularly in children, the signs of tumour—both general and focal—are prone to develop earlier and to become more clear cut than is the case in elderly persons, in whom diagnosis is accordingly apt to be more difficult. Probably several factors contribute to this difference.

In elderly persons the range of possible diagnoses is wider than in children in whom the many and often perplexing pictures of cerebral arterial disease do not present themselves. Again, tumours at the frontal end of the brain are comparatively rare in children. The frontal glioma and the meningioma are tumours of adult life. From their situation they give rise to indications of raised intracranial tension late, while the focal symptoms arising from this part of the brain are readily capable of misinterpretation. Therefore, peculiarities of tumour incidence at the different periods of life tend to accentuate the difficulty mentioned. Further, it seems that a brain which has undergone the changes inseparable from advancing arterial degeneration is not the clean slate upon which a tumour may make its mark that the brain of the younger individual is.

In children, on the other hand, tumours in the posterior fossa probably outnumber supratentorial tumours. As a result the development of internal hydrocephalus and the appearance of signs of raised intracranial tension develop early and betray the presence of tumour in an unequivocal manner.

Whatever be the value of the factors thus suggested, it remains true that pressure symptoms tend to be more markedly delayed in elderly than in young subjects, while focal symptoms are prone to have a blurred and indistinct character in the former and become most clear cut and complete in the latter.

The Production of Raised Intracranial Pressure.

(a) *Normal intracranial pressure.* The mechanism of production of raised intracranial pressure must wait for full understanding upon a more complete knowledge than we yet possess of the factors concerned in the maintenance of normal intracranial pressure. At present many fundamentally important physiological points are in dispute; such, for example, as the sites of formation and absorption of the cerebrospinal fluid (Cushing and Weed (43)). The following summary represents the most widely accepted body of opinion upon the physiology of normal intracranial pressure: arterial blood enters the skull at a pressure that ranges from 1,600 mm. of water (systolic) to 1,100 mm. (diastolic), and leaves in a non-pulsatile flow at a venous pressure that varies according to the posture of the individual from zero to about 150 mm. of water. The arterial pressure, of course, is not transmitted to the intracranial contents, and the pressure within the brain and in the subarachnoid space; that is, the intracranial pressure approximates closely to the venous pressure, and ranges from 80 to 150 mm. of water. This pressure is slightly higher than in the dural venous sinuses, but it cannot well exceed the pressure in the veins or these would be compressed under normal conditions.

In addition to the blood that circulates within the skull and brain, two processes of tissue-fluid formation occur; namely (i) the formation and absorption of cerebrospinal fluid, and (ii) the formation and absorption of tissue-fluid within the brain, that is, in the perivascular and other spaces ('intramedullary canalicular system', Weed (158)). These two spaces communicate on the surface of the brain where the perivascular channels open into the subarachnoid space. How rapidly osmotic and hydrostatic pressure variations in the fluid of one system are equalled throughout the other is not known, but that such an equalization does occur is clear from the observations of Weed and McKibben (157) upon the effects of the intravenous injections of hypertonic saline solutions. Probably a main function of the cerebrospinal fluid is to provide a water-bed for the brain and cord, that of the other fluid is to act as a medium of metabolic exchange between brain and blood-stream. The fact that the two systems communicate indicates that the pressure in brain and subarachnoid space is the same, and suggests further that these two systems cannot be regarded as physiologically altogether distinct (Fremont-Smith (67), Fremont-Smith and Kubie (68), Howe (95)).

(b) *The cerebrospinal fluid* may be regarded as a protein-free dialysate (Mestrezat) from the choroid plexuses, in osmotic equilibrium with the plasma except in respect of its protein content to which the capillary wall is impermeable. The formation of the fluid is a function of the hydrostatic pressure within the arterial capillaries of the plexus. The fluid emerges from the ventricular cavities to fill the subarachnoid space, and is reabsorbed into the blood through the arachnoid villi which penetrate the dural sinuses. This return depends upon the relatively low hydrostatic pressure within these sinuses; the conditions being the reverse of those which determine the formation of the fluid. This process differs from that by which tissue-fluids elsewhere in the body are formed and absorbed only in that a specialized structure, the choroid plexus, is concerned in the formation and other specialized structures, the arachnoid villi, in the absorption of the cerebrospinal fluid. The formation and absorption of the tissue-fluid within the brain depend upon the same osmotic and hydrostatic factors concerned in the case of the cerebrospinal fluid, though here no specialized structures are involved, the process occurring at the arterial and venous capillaries respectively in and upon the brain. The products of brain metabolism contained in this fluid reach, and are carried off by, the cerebrospinal fluid which they reach by the perivascular spaces. It may be mentioned here that some observers (Hassin (85)) believe that the cerebrospinal fluid is formed in the same way and in the same situations as the fluid now under consideration, while others (Dandy and Blackfan (49), Howe (95)) believe that it is also absorbed through venous capillaries of the brain and not through the arachnoid villi.

If this be so, then we have a single extravascular fluid system and not two separate systems as suggested above. The question is one that still awaits a satisfactory solution.

Within wide limits the pressure in brain and subarachnoid space is independent of intracranial arterial pressure, but it is closely dependent upon the venous pressure.

(c) *The dural sac.* The cranial dura forms a rigid sac, but the spinal dura is capable of some distension. For the purposes of a consideration of raised intracranial pressure, however, we may regard the dural sac and the contained subarachnoid space as approximately fixed in volume.

It is usual to regard the brain as incompressible, but from what has been said of the intramedullary canalicular system and its communication with the subarachnoid space, it is clear that the brain as a whole may be compressed not only by the expression of its contained tissue-fluid, but also by that of its venous blood.

(d) *Raised intracranial pressure.* In view of the rigidity of the skull, a disturbance of pressure equilibrium within it is readily caused when a growing tumour is added to its contents. From the various situations in which a tumour may arise and the different distortions of the brain found *post mortem* in such circumstances, it seems unlikely that the factors initiating a disturbance of intracranial pressure are always the same (Brain (17), Stopford (149)).

Room for the expansion of a tumour must be found by the expulsion of the fluids at lowest pressure within the skull; namely, the cerebrospinal fluid and venous blood. This process of expulsion may, at its onset, (i) meet with no mechanical obstruction, or (ii) it may from the onset be met by partial or complete obstruction when a tumour arises in certain situations. Each of these conditions may be considered in turn.

(i) If we take the case of a tumour within one cerebral hemisphere, the local enlargement of the hemisphere produced by the growth of the tumour will lead to the expression of tissue-fluid and of venous blood from the surrounding brain. The volume of the venous channels being greater than that of the arteries, the veins can be compressed until their volume falls to that of the former without congestion arising, while the absorption of cerebrospinal fluid will also remain free. In time the venous outflow becomes restricted, the venous pressure rises and fluid absorption becomes correspondingly impaired. Immediately around the tumour the veins are obliterated, those more remote are congested. For a time the dural partitions, falx and tentorium, confine this rise of pressure to that section of the cranial cavity in which the tumour lies, but ultimately the falx is deflected and the brain tends to herniate through the tentorial opening and beneath the lower margin of the falx. Displacements and distortions of the brain-stem and of the ventricles ensue, and the pathway of the cerebrospinal fluid becomes obstructed. A mechanical factor is now added to the hydrostatic one and cerebrospinal fluid absorption becomes progressively impaired. The raised venous pressure tends at the same time to cause an increased fluid formation from the choroid plexuses. Thus, the intracranial contents—tumour, blood, cerebrospinal fluid—gradually increase in bulk, and the raised intracranial tension characteristic of tumour results.

(ii) When a tumour is so situated, beneath the tentorium or at the base of of the brain, that it obstructs the free pathways of the cerebrospinal fluid and prevents its absorption, a rapid rise of intracranial tension ensues. Such an obstruction may occur at the foramina of Monroe, the third ventricle, the aqueduct, the foramina of the fourth ventricle, or at the tentorial opening. Here the mechanical factors that ensue secondarily in the case just considered are established from the outset, and the rise of intracranial pressure tends to be more rapid in these circumstances.

Mott and Barrett (115) suggested that obstruction of the great vein of Galen might initiate a rise of intracranial pressure, by raising the venous pressure in the choroid plexus and thus causing an excessive formation of cerebrospinal fluid. Recently Stopford (149) has returned to this view with a slight modification. He suggests that deflection of the falx, or a raising of the tentorium by tumour, causes a kinking of this vein where it enters the straight sinus, and thus puts in motion the mechanism invoked by Mott. It is probable, however, that a tumour of sufficient dimensions to cause such deflections of the dural sinuses must already have seriously overset intracranial pressure equilibrium, and thus obstruction of the great vein of Galen produced in this way can hardly be other than an occasional and late factor in still further increasing an intracranial pressure already risen beyond physiological limits.

In cases of tumour the pressure in the dural sac, as measured in the spinal theca by lumbar puncture, may range from 500 to 1,000 mm. of water.

In view of the circumstances thus briefly summarized, it appears unlikely that a simple generalization can cover all the possible ways in which the pressure equilibrium within the skull may be upset.

(e) *The signs and symptoms of increased intracranial pressure.* These include headache, vomiting, papilloedema, slowing of the pulse-rate, and a slowly progressive blunting of mental alertness and capacity passing to stupor and terminal coma.

Although it is widely stated that the situation of the headache in a given instance bears some relation to that of the tumour, any such relationship may be difficult to establish. It is true that subtentorial tumours frequently cause occipital headache, but so also may frontal tumours, while the converse may obtain. Similarly, a tumour of the cerebral hemisphere may cause pain which is referred to the overlying portion of the skull. A degree of false precision is easily lent to statements on this point by the tendency to make some generalization, and subsequently to stress all cases that fall into line with it, but to refrain from comment upon those that do not. In all cases the headache is apt to be most severe in the morning on awaking, to be paroxysmal, and to be aggravated by movement or exertion.

It is customary to invoke tension of the dura as the cause of tumour headaches (Dott (55)), but from what has already been said it is clear that *in the intact skull* the cranial dura cannot be under tension. Further, it has been

observed that the dura is insensitive to stretching by the surgeon (operating under local anaesthesia), and that it is only when the meningeal vessel walls are handled that pain ensues. Elsberg (57) believes therefore that it is in variations in intraventricular pressure that we must seek the cause of the headache of raised intracranial pressure. Vomiting is a common, but inconstant, concomitant of raised intracranial pressure, appearing earlier and proving most severe in association with subtentorial than with supratentorial tumours. Here, also, the generalization that it is commonly projectile in character is apt to be misleading, for in many cases it is preceded and accompanied by severe nausea and retching.

Papilloedema has been shown by Paton and Holmes (119) to be a venous engorgement and oedema of the nerve-head, and they believe it to be produced by an obstruction to the venous return from the eye. The central retinal vein leaves the optic nerve behind the eye and crosses the subarachnoid sheath of the nerve. This sheath is distended by cerebrospinal fluid under pressure and compresses the vein. Horsley (94) believed that the prior appearance of papilloedema in one eye had a localizing value and commonly occurred on the same side as the tumour. In an analysis of a large series of cases Paton (118) failed to confirm this view. The rate of development of papilloedema varies widely from case to case, being greatest in those cases in which hydrocephalus develops early and rapidly. A slowly increasing papilloedema may be present for a long period before there is appreciable failure of vision. In other cases, on the contrary, an early and almost sudden total loss of vision may occur. The appearance of phases of transient blindness, usually brought on by sudden exertion, is the herald of visual failure.

Slowing of the pulse and mental obfuscation may be regarded as terminal phenomena, and with their appearance the patient, unless relieved by surgical intervention, is near his end.

Various series of statistics have been published to illustrate the sequence of appearance and the relative frequency of these various signs of raised intracranial tension. Not all of them are present in every case; indeed, all may be lacking, especially in elderly persons, until the terminal stage of the illness. Thus it is that the statistics vary no less widely than the events they summarize, and no good purpose would be served by citing them.

As to the sequence in which localizing and general pressure signs make their appearance, it may be said that those tumours that are so situated as to produce an early hydrocephalus might be expected to give rise to pressure signs first. This is the case with many mid-line tumours at the base of the brain and in the region of the third ventricle. With the last named it is only when by expansion the tumour encroaches upon and compresses structures lying near or bounding the ventricle that focal signs develop. Extra- and intra-cerebellar tumours, on the other hand, though they are associated with marked hydrocephalus in most instances, nevertheless characteristically produce localizing signs early.

But other factors than hydrocephalus may determine the precedence of general over focal symptoms. The slow-growing meningiomata that arise commonly in the upper half of the skull, even when they produce gross distortion of a hemisphere, may betray their exact situation only very late in their history and after well-marked pressure signs are present.

It seems possible, also, that with the slow-growing fibrillary astrocytoma, functioning nerve-cells and fibres may survive within the area of tumour infiltration for some time and thus give no indication of the tumour that is developing in their midst.

Therefore, just as diverse factors may determine the onset of a rise of intracranial pressure, so also the order of precedence in time of general and focal symptoms is governed by more than one factor.

Generalized Epileptiform Fits as an Initial Symptom of Tumour.

Over half a century ago Hughlings Jackson first described those focal fits that now bear his name. The forms that these may take and the significance attaching to them are so thoroughly embodied in medical thought that there is now little chance of their meaning being overlooked. It appears to be less widely recognized that generalized epileptiform fits, indistinguishable from those of idiopathic epilepsy, hold a prominent place in the symptomatology of intracranial tumour, and may, moreover, for a long period be the sole manifestation of the presence of such a tumour. Every neurologist is familiar with cases that, having for months or even years been quite indistinguishable from ordinary epilepsy, in the end rapidly develop the signs of intracranial tumour, and he has learned to keep this possibility in mind whenever fits make their first appearance at an age later than that at which epilepsy ordinarily develops.

It is remarkable in the circumstances that no clear and explicit statement to this effect is to be found in text-books of medicine, either under the heading of epilepsy or that of intracranial tumour, and it is to the lack of this that, when epileptic fits make their appearance in an otherwise healthy middle-aged subject, intracranial tumour is the last possibility to be considered, though it is the most likely explanation of their occurrence.

The fits in question have no precise localizing value and they bear no distinguishing features. They may occur singly at long intervals over a period of months or years. Not uncommonly an apparently healthy subject enters suddenly into status epilepticus for some hours, makes a complete recovery, and enjoys a period of normal health before single fits or another phase of status ensures. Ultimately such a fit or series of fits leaves residual paralytic symptoms, and the signs of intracranial tumour develop apace.

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The statement that they have no localizing value calls for some qualification. As an initial manifestation of tumour they occur usually in association with tumours within a cerebral hemisphere, though there are examples of pituitary, suprapituitary, and basal tumours that have presented fits as an

initial symptom. They do not occur thus in the case of cerebellar or brain-stem tumours. Further, the generalization may be made that their occurrence suggests a slow-growing glioma as the most likely variety of tumour present, though a few cases of meningioma have been reported to show this sequence of events.

We cannot regard the occurrence of fits in these circumstances as indicative of raised intracranial pressure, nor as a measure of the size of the tumour. They are quite commonly absent from those subtentorial tumours that produce the most severe pressure signs, and when raised pressure ensues in a case in which they have occurred, they show no tendency to increase in severity or frequency. Further, the great lapse of time that may ensue between their first appearance and the development of pressure signs is another indication for not regarding these fits as among the signs of raised intracranial pressure.

What is probable is that they are caused by local and transient disturbances in the circulation within a hemisphere. The role of anaemia, and of the associated anoxaemia, in exciting convulsions is well known. It may be said, therefore, that generalized epileptiform fits making their first appearance in an otherwise healthy subject in the fourth or fifth decades of life should at once raise a suspicion of intracranial tumour. In the case of general paralysis, other indications of the malady are to be found on examination, and this is true also of the fits of renal disease. In more elderly persons cerebral vascular degeneration has to be considered, while it is true that in rare instances ordinary epilepsy does begin during the period of life specified above. These minor qualifications do not detract from the importance of the generalization just made, and in all individuals comprehended by it careful and repeated examinations of the fundi, the visual fields, and the nervous system in general are necessary.

False Localizing Signs.

In 1904 Collier (21) drew attention to the relative frequency with which palsies of the sixth and third nerves may be produced by tumours which are anatomically remote from them. Such palsies result from the displacements and distortions of the brain produced by the tumour and are appropriately spoken of by Collier as 'false localizing signs'. It is the sixth nerve that is most commonly affected in this way, and diplopia from unilateral or bilateral weakness of the external rectus is a frequently observed concomitant of raised intracranial pressure from tumours in various situations; for example, a diplopia of this kind is the rule in cases of medulloblastoma cerebelli.

On the other hand, Collier points out that affections of these nerves appearing early in the clinical course of tumour, and especially as components of alternating hemiplegia, have the greatest localizing value. He explains the occurrence of these false localizing signs as due to the herniation of the cerebellum and medulla through the foramen magnum in the course of a rising

intracranial pressure. This pushing downwards of structures 'will cause stretching of those nerves attached to the medulla, in proportion as they are directed antero-posteriorly, and take a straight course between their attachments to the dura and their origin from the medulla, and of these the sixth nerve will be most affected, and afterwards the third, seventh, and fifth in that order. These nerves will not only be stretched, but are subject to the increased pressure also, and they may accordingly cease to function.'

In 1911 Cushing returned to this subject (26) and expressed the view that stretching of a cranial nerve was of itself inadequate to put it out of function, and cited the extreme stretching and elongation of the seventh nerve in cases of auditory nerve tumour, with the long delayed and relatively trivial impairment of function associated therewith. Further, he found on examination of brains from tumour cases that during life had presented signs of raised intracranial pressure together with sixth and third nerve palsies of false localizing significance, that the ventral surface of the pons was deeply indented by the basilar artery and its lateral branches, and also that the latter commonly ran superficial to the nerves. The nerves thus overlaid were seen to be deeply indented and bent out of their course by the arteries, and on microscopic examination were found to show degenerative changes.

Cushing suggested that strangulation of the sixth nerves by overlying arteries (anterior inferior cerebellar artery) was the mechanism of production of the common squint and diplopia of intracranial tumour. The case of the third nerve was not so closely investigated, but a similar factor was invoked in this instance.

It is known that in certain cases of pontine glioma, the third nerve may show signs of impaired function (ptosis, squint), although not directly involved by the tumour. The antero-posterior length of the pons is not infrequently increased by the 'hypertrophy of the pons' produced by this variety of tumour; a distortion that has the effect of pulling the diverging posterior cerebral arteries downwards on to the ventral surface of the pons and out of their normal position at the junction of crus and pons. The emerging third nerve which lies immediately caudal to the artery in this situation is sharply bent back and pressed down against the pons by the artery and thus 'strangulated' in the same manner as the sixth nerve. Dr. Greenfield has drawn the attention of the writer to this possible cause of a falsely localizing third nerve lesion in cases of pontine glioma.

More recently Wolff (164) has advanced another explanation of sixth nerve palsies. He points out that if antero-posterior stretching, as suggested by Collier, were responsible the frail trochlear nerve could hardly escape. By an appropriate parasagittal section of the head of the cadaver he was able to expose the whole antero-posterior course of the sixth nerve and found that, in fact, this is not a straight course but an angular one. At first the nerve runs almost vertically upwards, slightly outwards and forwards under the dura on the back of the petrous bone. Reaching the sharp upper edge of this it bends

forwards under the petro-sphenoid ligament at a right angle to pass towards the cavernous sinus. In these circumstances a downward movement of the pons under the influence of raised pressure within the skull will not only stretch the nerve but will do so over this sharp bony edge, with resulting interruption of conduction.

Bruns (18) cites Wernicke as having given still another possible explanation of false-localizing cranial nerve palsies; namely, lateral displacement of the brain-stem which thrusts the crossed cranial nerves against the sharp dural edges of their foramina of exit. Less widely recognized than the foraminal herniation of the cerebellum and medulla is the herniation of the uncus down through the tentorial opening. This displacement and distortion of the temporal lobe may compress the homolateral third, fifth, and sixth nerves as these pass forwards, and doubtless the occasional ptosis that accompanies temporal lobe tumours arises in this way.

Groeneveld and Schaltenbrand (81) and Kernohan and Woltman (101) have drawn attention to yet another displacement of the brain that occasionally produces a false localizing sign; namely, homolateral hemiparesis with appropriate reflex changes, in tumours of one cerebral hemisphere. Lateral pressure not only produces herniation of the uncus, but may also displace the crura cerebri towards the opposite side. In these circumstances the lateral margin of the crossed crus is pressed against the sharp tentorial edge and is severely indented. This indentation is not only readily visible, but is accompanied by degeneration of nerve-fibres beneath the deformity. In this way arise homolateral pyramidal tract signs in temporal lobe tumours.

Another example of remote focal signs is the cerebellar symptomatology that occasionally occurs with frontal and pituitary tumours, and also with third ventricle tumours, where it is presumably the result of pressure exerted backwards by a tumour lying anterior and superior to the cerebellum.

Some Localizing Symptom-complexes.

It is probable that in the field of localizing diagnosis the past twenty years have not seen advances comparable with those that have been made in the pathology of intracranial tumour. A number of noteworthy contributions to clinical knowledge have certainly been made; notably in the case of tumours in the pituitary region. But in other instances the clinical descriptions of twenty and more years ago remain unequalled for completeness and precision.

The addition of radiography with its applications of ventriculography and encephalography is possibly in large measure responsible for an appreciable waning of confidence and of interest in purely clinical study, and for a falling off in the quality of clinical reports that are evident in some recent papers. How far some observers have come to dispense with clinical investigation may be seen in the case of tumours of the pineal body. These are recognized by the disorders of pupillary action and of ocular movement that, sooner or later, they

invariably produce. An excellent account of these was given in 1910 by Howell (87) in this country and by other writers elsewhere. Nevertheless, Dandy (48) goes so far as to say that ventriculography affords the sole means of localizing these—and most other—tumours, prefacing this opinion by a most inadequate reference to the ocular signs in question. In so far as this extreme view represents a widespread trend of thought, it is one plainly detrimental to the increase of clinical knowledge, and it appears to require that we shall jettison our accumulated clinical information in favour of a new method, the dangers and narrow scope of which are obvious. It cannot be long before a sounder balance of opinion is struck, and ventriculography and allied procedures will come to take their only legitimate place as useful additions to careful clinical investigation.

Within the past few years there have appeared numerous clinical analyses of the symptom-complexes produced by tumours in certain specified situations within the cerebral hemispheres, within the third and fourth ventricles, in the chiasmal, and in other regions. Also a number of newly observed signs of localizing significance have been recorded. To deal adequately with all these is not now possible, and attention will there be mainly directed to the less familiar of these symptoms and symptom-complexes.

(a) *Tumours of the pituitary region.* Three elements enter into the complete picture of a tumour in this region; (i) neighbourhood signs, (ii) signs of raised intracranial tension, and (iii) disorders of pituitary function. Not all of these are necessarily present in a given case, indeed, general pressure signs are frequently wanting.

The pituitary adenoma, the hypophyseal duct tumour and the suprasellar meningioma all have approximately the same major anatomical relationships, yet it is usually possible to differentiate these three clinically on grounds of physical signs, age incidence and history, and radiological appearances in the skull.

(i) *Neighbourhood signs.* These include the chiasmal syndrome and, in the case of suprasellar tumours, the signs of encroachment on the third ventricle. Of the chiasmal signs, visual defects and ophthalmoscopic appearances are the most significant and depend upon the contiguity of tumours in this region to the optic nerves, chiasma, and tracts. These relationships vary somewhat from case to case. Usually the anterior border of the chiasma rests upon the sellar diaphragm, and in this case the upwardly directed pressure of a tumour within the sella involves the decussating and macular fibres and causes a bitemporal hemianopia. In other cases one or both optic nerves anterior to the chiasma may be compressed. In these circumstances there is progressive blindness in one eye, with the development of a temporal hemianopia in its fellow. Less commonly, pressure is exerted upon one optic tract posterior to the chiasma, in which case an homonymous hemianopia results.

In practically every case of tumour within the sella, the optic nerve sheath is compressed, and the development of a papilloedema is thus rendered impossible.

Cushing and Walker (41, 42) have traced the development of the bitemporal hemianopia which is the most common field defect in tumours of this region. The initial defects are the appearance of a paracentral scotoma in the upper temporal quadrant and of a sector defect immediately peripheral to this. The latter advances slowly from the periphery towards the scotoma and joins it. Colour vision recedes on the same fronts as form vision; next the lower temporal quadrant is invaded from the periphery, and finally the temporal field is completely lost. In suprasellar tumours, on the other hand, pressure is exerted from above downwards and the decussating fibres from the upper temporal quadrants of the retinae are first compressed, so that the lower temporal quadrant of the visual field is the first to go. Finally the nasal fields are lost and complete blindness ensues, with dilatation and immobility of the pupils. This process usually begins earlier (Cushing and Walker (41, 42), Holmes and Sargent (75)) in one eye than in its fellow, so that when the patient first comes under observation one eye may be totally blind while its fellow exhibits the earlier stages of invasion of the temporal field.

Ophthalmoscopic appearances. Following on the development of the field defects, and a result of the same process of compression, a progressive pallor of the optic disks appears, a primary optic atrophy. Greater familiarity with the clinical picture of hypophyseal duct tumour shows that, while in intrasellar duct tumours primary optic atrophy is the rule, papilloedema occurs with considerable frequency. Beckmann and Kubie (16) have pointed out that this is particularly the case in children and adolescents—in whom indeed this variety of tumour is most commonly seen. Thus in twenty-one cases of hypophyseal duct tumour analysed by them, papilloedema was present in four of their six juvenile cases and in one adult case, while primary optic atrophy was present in two of the six juvenile cases and in ten of the fifteen adult cases. In this respect, these tumours stand in contrast with the adenomata and with the suprasellar meningiomata which are rarely found in association with papilloedema. However, in suprasellar meningioma a mild papilloedema may be seen superimposed upon a developing primary optic atrophy. In these circumstances the severe impairment of visual acuity and the field defect betray the presence of the underlying primary atrophy.

When the interpeduncular space is encroached upon by an expanding sellar or suprasellar tumour, structures lying within or bounding this space may be compressed and so produce additional focal signs. Thus, compression of the third and sixth nerves give rise to diplopia, squint, and ptosis, of the fifth nerve to neuralgic pain in the face, of the cerebral peduncles to unilateral or bilateral weakness and changes in the reflexes, and of the temporal lobe to uncinate seizures. Personality changes indicative of compression of the frontal lobes, anosmia, and unilateral or bilateral exophthalmos have also been recorded. Recent analyses of the clinical pictures of tumours in the pituitary region tend to stress the predominance of hypophyseal duct tumours in the production of these phenomena, and the relative infrequency of their appearance in connexion

with pituitary adenoma and suprasellar meningioma. This emphasis is just in respect of the early clinical stages, but as Cushing's monograph (27) on pituitary disorders shows, all three varieties of tumour come to produce them in the later stages of growth and expansion.

(ii) *Signs of raised intracranial tension.* As has been mentioned, these are most commonly found with hypophyseal duct tumours. As these expand in an upward and backward direction they encroach upon the space normally occupied by the cavity of the third ventricle and thus give rise to internal hydrocephalus. Those intrasellar tumours which overflow the sella and expand above and around this may also in course of time produce similar results. With the development of hydrocephalus, headache, vomiting, and, in the case of duct tumours that have not obliterated the optic nerve sheaths, papilloedema ensue.

While the chromophile adenoma that gives rise to acromegaly often produces intense bitemporal headaches, it is doubtful whether the other varieties of tumour in this region give rise to headaches of localizing significance.

(iii) *Disorders of pituitary function.* In considering these disorders in relation to tumour, it has to be remembered that in the case of all tumours that invade the interpeduncular space and encroach upon the space occupied by the third ventricle, structures other than the pituitary body are subjected to compression; in particular the nuclei of the floor and walls of the third ventricle, the hypothalamic nuclei. Tumours do not serve, therefore, to differentiate pituitary from hypothalamic disorders of function. Further, there is considerable controversy as to the distribution of function between these two structures, but since new growths throw little light upon the matter, no detailed consideration need be given to it, and for the present we may speak of 'hyperpituitarism' and 'hypopituitarism' without reference to this problem. The 'pituitary' disorders in question include anomalies of growth, of sexual development, of metabolism, and of sleep, and it is apparent that the signs of the two first named must vary according to the age of the patient.

While pituitary adenomata are tumours of adult life, hypophyseal duct tumours are congenital in origin and commonly give rise to symptoms before adolescence. Further, while adenoma of the acidophile cells (chromophile adenoma) invariably gives rise to signs of anterior lobe hyperactivity (gigantism rarely, acromegaly commonly), all other tumours compressing the pituitary body; namely, chromophobe adenoma and hypophyseal duct tumour, give rise to 'hypopituitarism'.

Chromophile adenoma, therefore, being a tumour of adult life produces acromegaly followed by the appearance of the chiasmal syndrome, and in time by that of the other localizing (interpeduncular) signs enumerated above. Owing to the common age incidence of this growth, gigantism is of rare occurrence.

Chromophobe adenoma and hypophyseal duct tumour, unlike the growth just considered, usually come under notice in the first instance on account of the chiasmal syndrome, or because (in the case of duct tumour) of signs of raised

intracranial pressure. The 'hypopituitarism' such cases commonly display is much less obvious than acromegaly, and consists in obesity, genital dystrophy, and—occasionally—diabetes insipidus and somnolence, a lowered metabolism and blood-pressure. These symptoms together constitute the 'dystrophia adipose-genitalis' of Fröhlich. Less commonly, pituitary infantilism (Lorain type) without obesity occurs, but the clinical picture described by Simmonds as due to infarction of the pituitary body does not arise as a result of new growth. In children, therefore, there is a failure of sexual pubescence, a greater or less degree of obesity, and sometimes somnolence and diabetes insipidus. Nevertheless, such children display no mental backwardness or deterioration. In adults, there is regression of sexual functions, amenorrhoea in women and loss of sexual desire and capacity in men, with the other symptoms just enumerated. As will subsequently appear, all these so-called signs of 'hypopituitarism' occur in cases of third ventricle tumour, in many of which there is no evidence of compression of the pituitary body.

The relatively uncommon *mixed cell adenoma* (Dott and Bailey (56)), as already mentioned, gives rise to a mixed clinical picture containing elements of hyper- and of hypopituitarism, a combination to which Cushing has given the name 'dyspituitarism'.

In *sellar meningioma*, all these 'glandular' signs are commonly absent and diagnosis rests upon the presence of the chiasmal syndrome in adults of over thirty years of age.

Primary glioma of the optic chiasma. Martin and Cushing (111) have reported seven cases of this condition in young children. The signs are primary optic atrophy, with rapid loss of vision in both eyes. A clear-cut temporal defect is not seen as in other tumours in this region, though the field defect does approximate to this form at onset. There is an absence of pituitary disorders. Unilateral exophthalmos sometimes occurs.

Finally, so-called toxic symptoms are not infrequent in duct tumours, though lacking in adenomata and sellar meningiomata. They are variously described and include febrile periods, headaches, symptoms suggestive of meningitis, urticarial rashes, and transient illnesses diagnosed as 'influenza'. Correlated with these are the striking toxic symptoms that may ensue upon operative interference with a duct tumour. They may make their appearance immediately after opening of the cystic tumour or may be delayed for one or two weeks. They include hyperthermia, delirium, vomiting, restlessness, muscular twitchings, and coma. In some fatal cases of the kind the temperature may rise to 107° before death (19).

This reaction appears to be a relatively common sequel of operation upon these tumours, and together with the technical difficulties of surgical intervention make the latter a hazardous adventure.

Radiological appearances in the skull. Pituitary adenoma causes a uniform deepening and ballooning of the sella with no marked deformation of its normal contour. Hypophyseal duct tumours cause absorption of the posterior clinoid

processes and impart a shallow open outline to the sella, the floor of which may be irregular. Further, shadows of calcareous nodules may be seen both within and above the sella. Suprasellar meningioma commonly causes no appreciable change in the sellar outline or dimensions, but occasionally some absorption of the posterior clinoid processes and shadows of calcification within the tumour may be seen. In glioma of the optic chiasma, Martin and Cushing report an enlargement forwards of the sella under the anterior clinoid processes.

All the foregoing observations may be briefly summarized in the following table.

	Adenoma.			Duct Tumour.	Meningioma.	Glioma of Optic Chiasma.
	Chromophobe.	Chromophile.	Mixed Cell.			
Age incidence	From adolescence onwards			From 10 years to early adult life	From 30 years onwards	In childhood usually
Fundus oculi	Primary optic atrophy			Papilloedema in children usually primary optic atrophy in adults	Primary optic atrophy	Primary optic atrophy
Visual fields	Bitemporal hemianopia			Bitemporal hemianopia	Bitemporal hemianopia	Bitemporal hemianopia going on to early blindness
	(occasionally homonymous hemianopia)					
Pressure symptoms	Absent, or late			Early and severe, except in adults	Absent, or late	Absent, or late
Glandular symptoms	Hypopituitarism	Hyperpituitarism to Hypopituitarism	Mixed	Hypopituitarism	Nil	Nil
Situation	Sellar			Suprasellar	Suprasellar	Suprasellar
Radiological	General enlargement and deepening of sella.			Shadows above and in sella. Sella shallow and with uneven floor	Commonly no change	Enlargement of sella forwards beneath ant. clinoid processes

(b) *Tumours of the third ventricle and pineal body.* Tumours encroaching upon the third ventricle, either by pressure and distortion from without or from growth within that cavity, sooner or later occlude the foramina of Monroe and the aqueduct of Sylvius, and thus produce internal hydrocephalus and raised intracranial pressure.

Hence, general pressure signs commonly afford the first indications when a tumour arises in this region, and a varying time elapses before focal signs are added thereto. The signs in question result from compression of structures

bounding the ventricle, and, if we are to judge from the nature of most focal signs, consist in impairment or loss of function. In the floor of the ventricle from before backwards lie the optic chiasma and tracts, the tuber cinereum with its infundibular recess and the hypophyseal stalk, the corpora mammilaria, the posterior perforated space, and the crura cerebri. Laterally the ventricle is bounded by the thalamus and hypothalamic region, and posteriorly by the aqueduct of Sylvius, the posterior commissure, the pineal body, and the tegmentum of the mid-brain.

Distension and occlusion of the third ventricle almost invariably produce, at some stage of the process, a group of symptoms already mentioned in connexion with tumour of the pituitary region, namely, obesity, sexual dystrophy, diabetes insipidus, and somnolence. Not all of these are present in every case. In addition to these other focal signs arise according to the site of origin of the tumour. Thus, tumours arising in the neighbourhood of the infundibulum may compress the chiasma and optic tracts and produce the visual field and ophthalmoscopic signs described in connexion with pituitary tumours. Hypophyseal stalk tumours sooner or later encroach upon the third ventricle from below and in front, and, as we have seen, cause either primary optic atrophy or papilloedema, together with the disorders of growth and metabolism enumerated above.

Tumours arising within the ventricle may, until the terminal stages of the illness, produce no other signs than those of raised intracranial pressure with one or more of the following symptoms: diabetes insipidus, obesity, sexual dystrophy, and somnolence. Tumours arising at the posterior end of the ventricle or in the region of the pineal body produce, in addition to general pressure signs, characteristic disturbances of pupillary action and of ocular movement. These develop in the following sequence: there is progressive dilatation of the pupils with failure of the light reaction, and later of the accommodation reaction. Impairment and then loss of upward movement of the eyes ensues, with impairment of downward movement and sometimes of conjugate deviation laterally. In these circumstances the attempt to look upwards may elicit a rhythmical convergence spasm (52). Nystagmus is also sometimes present. These disorders are probably referable to compression of the supranuclear centres in the roof of the mid-brain. Added to them, ptosis, squint, and diplopia may occur. Wilson (161) has further recorded that in such cases, in association with accesses of coma, a dilatation and immobility of the pupils with marked eccentricity of the latter may be seen. In some cases, therefore, an Argyll-Robertson pupil may occur, but this differs from the phenomenon as seen in cases of neurosyphilis, in that whereas in tumours in this region the pupils are dilated, in neurosyphilis myosis is the rule, and irregularity of the pupils and atrophic changes in the iris accompany the loss of light reaction. In this connexion it may be mentioned that, as originally described by Argyll-Robertson, the phenomenon that bears his name consisted not only in a loss of the light reflex, but also in myosis.

In any given instance the site of origin of the tumour has to be inferred from the sequence in which these various localizing phenomena appear, and from the relative predominance which any one or more of them may obtain. Thus, a combination of signs of internal hydrocephalus and raised intracranial pressure with somnolence, obesity, diabetes insipidus, and genital dystrophy points to the floor of the ventricle as the situation from which the tumour is developing; while internal hydrocephalus associated with marked pupillary and ocular disorders indicates a tumour at the posterior end of the ventricle and in the pineal region. Tumours arising in the roof of the ventricle may not give rise to localizing signs until late in their course. Associated with extreme distension of the ventricle, disorders of balance and of co-ordination indicating involvement of cerebellar mechanisms may be observed. But such signs never appear as initial phenomena, and seldom develop into a full-fledged cerebellar symptom-complex.

With reference to the group of symptoms that includes obesity, genital dystrophy, diabetes insipidus, and somnolence, it is clear from what has been said that one or all of these may accompany either pituitary, suprapituitary, or third ventricle tumours. They are the symptoms spoken of in connexion with the two first named as indicating 'hypopituitarism'. Within the past decade an extensive literature, both clinical and experimental, has been devoted to the question of the parts played in their production by the pituitary body and by the hypothalamic nuclei. Cushing (36), and Bailey and Fulton (71) have given full summaries of the subject, and to their contributions the reader may be referred for details, only a brief statement can be made here.

The most widely accepted view is that acromegaly and sexual dystrophy are true anterior lobe symptoms, the first arising from hyperactivity of the acidophile cells, the second occurring both with hyper- and hypo-activity of this structure. In respect of obesity, diabetes insipidus, and somnolence the evidence, both clinical and experimental, is not yet conclusive, though it appears certain that these disorders can occur with hypothalamic lesions which apparently leave the pituitary body intact. It has been suggested that the posterior lobe of the pituitary body and the hypothalamic nuclei constitute a neuro-hypophyseal mechanism, and that the disorders in question may result from a lesion of either component. Unfortunately, the literature is rendered unnecessarily confusing from the widespread omission of writers to draw any distinction between the normal function of a part and the symptoms resulting from a lesion of that part, and the well-known teachings of Hughlings Jackson on the dissolution of function are generally neglected.

This is readily illustrated in connexion with the somnolence that so frequently accompanies third ventricle tumours. It has long been known that sudden transient accesses of sleep resembling narcoleptic attacks, or sustained drowsiness or even sleep, may accompany basal tumours. It appears, however, that under the heading of 'sleep' some writers include those accesses of deep coma that have been referred to in connexion with some observations made by

Wilson in a case of ball-tumour of the third ventricle. These attacks of coma were preceded by a period of drowsiness and mental confusion with the unnoticed passage of urine. The patient then became deeply comatose. To speak of such a condition as sleep is to misuse words. A freely movable tumour within the ventricle seems to be associated with the condition, and in all probability the factors responsible are the sudden blocking of the aqueduct and the sudden development of raised pressure within the ventricle.

Many writers express a belief in the existence of a localized 'sleep centre' in the hypothalamic region, which they hold responsible for the disorders of sleep mentioned. But even should such a centre exist, and the work of Pawlow affords no encouragement to so naïve a notion, its destruction or inactivation by a tumour cannot rationally be invoked to explain excessive sleep, for this is a symptom of a lesion and not the normal function of the part in question. Yet numerous observers, having localized to their satisfaction the site of a destructive lesion from which sleep ensues, proceed with complete inconsequence to label this site as a 'sleep centre'. Even in Fulton and Bailey's paper (71) we find used as synonymous such expressions as 'the lesion responsible for hypersomnia' and 'the region responsible for hypersomnia'. It is clear that no true physiology of the hypothalamus can be elucidated until the confusion of thought underlying these errors is eradicated. An interesting commentary upon these theories of a sleep centre is found in the constancy with which marked drowsiness is seen as a symptom of tumours involving the corpus callosum.

Finally, in connexion with a few recorded cases of pineal tumour in pre-adolescent boys (Haldemann (83)), in addition to the localizing signs enumerated above, a condition of premature sexual maturity has been observed.

(c) *Tumours of the fourth ventricle.* The pathological varieties of tumour commonly seen in this situation are, in order of frequency, medulloblastoma, ependymoma, and choroid papilloma. All have their main incidence during childhood. The clinical picture presented by medulloblastoma may be taken as typical of tumours in the fourth ventricle. After a short initial period of headache, which is commonly occipital, the signs of raised intracranial pressure—due to hydrocephalus—develop rapidly, and associated with them is usually a bilateral abducens palsy. Unilateral facial weakness is common and dilatation of the pupils may occur. A later sign is tinnitus with deafness. Added to these are indications of cerebellar disorder, ataxy of gait, less pronounced ataxy of the upper limbs. Nystagmus may be absent throughout the course of the illness. In some instances the ataxy is bilaterally symmetrical from its onset, but in others it predominates on one side for a time. There may also be rigidity of the neck muscles and Kernig's sign, and when to these signs are added loss of the tendon-jerks, fretfulness, and wasting, a diagnosis of tuberculous meningitis may be made. In other cases the tendon-jerks and plantar reflexes remain normal, while in yet others spasticity and corresponding reflex alterations have been recorded. The clinical course is a rapid one, and may be punctuated by cerebellar seizures of the kind originally described by Hughlings

Jackson. The cerebellar tumours of childhood are commonly of this variety, which is comparatively rarely seen in adults in whom cystic astrocytoma is the tumour usually found in this region. The tumour may infiltrate the pia-arachnoid over the cerebellum and at the base of the brain. In these circumstances other cranial nerves than those already specified may be involved, and the clinical picture takes on some of the characters described under the heading of the 'metastatic syndrome' of secondary carcinoma. Several of the cases reported by Firor and Ford (63) under the title of 'gliomatosis of the leptomeninges' appear to have been examples of medulloblastoma with meningeal infiltration.

The frequent absence of nystagmus in medulloblastoma has been explained as due to the median situation of the tumour, but, in spite of the latter, the cerebellar symptomatology although bilateral is not invariably equally pronounced on the two sides, and it may be that nystagmus is present in those cases in which this asymmetry of ataxy is marked.

The clinical picture of fourth ventricle ependymoma (5, 62) resembles that already described in its general features, though it may be much more gradual in evolution. While, as we have seen, medulloblastoma tends to invade the pia-arachnoid, the ependymoma tends to grow downwards through the foramen magnum and to form a mass compressing the upper segments of the spinal cord. It may also spread around the pons and fill the basal cistern. It is probably in virtue of this extra-ventricular spread that a spastic condition of the lower limbs may develop, with corresponding alterations in the reflexes of these limbs.

Papilloma of the choroid plexus of the fourth ventricle is comparatively rare, and, in the single case that has come under the writer's observation, the signs were those of internal hydrocephalus, of 'hypopituitarism', with but slight indications of cerebellar disorder. To what extent this is a typical picture is not easy to say.

It may be mentioned here that the common cerebellar cystic astrocytoma of childhood produces a clinical picture that in its components resembles that of medulloblastoma (Cushing (37)), but differs in that the clinical course of the former is slower and is not infrequently intermittent. Thus Cushing states that a phase of morning headache with vomiting may be followed by a long period of apparently normal health before further development of signs and symptoms. Further, the tendency of the cyst to expand laterally may lead to an asymmetry of the localizing signs. In general it appears that, as with other slow-growing tumours, the size of the lesion as revealed at operation is commonly greater than the intensity of the localizing signs have indicated. Indeed, cerebellar seizures may appear at a time when these signs are not fully developed.

(d) *Tumours of the corpus callosum and frontal lobe.* For several reasons it is convenient to consider tumours in these adjacent regions together. The most frequently occurring tumour of the corpus callosum is the glioblastoma which commonly invades the frontal lobe in the course of its growth. Further a comparison of the recorded symptom-complexes of callosal and of frontal

tumours reveals that they have much in common, and it is doubtful if a clean picture of corpus callosum lesion is ever presented by a new growth. On the other hand, owing to the frequency with which meningiomas overlie and compress the frontal lobe, what we may regard as an uncomplicated picture of a frontal lobe lesion is not infrequently observed.

It is commonly believed that the recognition of frontal lobe tumours is rendered peculiarly difficult owing to the absence of localizing signs. It would probably be more accurate to say that, in fact, such signs are not wanting, but that they differ essentially in quality from those arising from tumours elsewhere in the brain, are more difficult of appreciation in their earlier stages, and as a consequence readily pass unnoticed.

This difference in quality consists in the fact that the characteristic localizing signs are psychical rather than somatic. They develop as a slowly progressive impairment of the patient's mental alertness and initiative. His emotional tone fades, he becomes apathetic, neither his feelings nor his intelligence are readily aroused, or if aroused not sustainedly. His memory for recent events deteriorates, his association of ideas is poor. As a consequence all his activities are restricted and slowed down. He takes longer in performing the daily details of life, some of his most ingrained habits fall from him, he becomes careless of his appearance, sits vacantly in his bath, and needs repeated urging to carry even the simplest routine act to a finish. In conversation he becomes extremely slow and monosyllabic, no adequate history can be obtained from him, and he displays no active co-operation. Part and parcel of this progressive obfuscation is an indifference to the calls of nature, he passes urine and faeces in his bed, or even in company—to the embarrassment of every one but himself. This form of incontinence is indeed one of the most constant and significant of localizing signs. Gradually his hebetude passes into drowsiness, a symptom that is even more pronounced in tumours involving the corpus callosum. Less commonly the mental state may be one of euphoria, or of mental exaltation and excitement. It is not to be supposed that these variations in the form of the mental disorder necessarily indicate differences of localization within the frontal lobe; it is more probable that they express the mental constitution of the affected individual.

In this connexion it may be mentioned that a slowly progressive blunting of mental acuity accompanies a rising intracranial pressure in most cases of intracranial neoplasm wherever situated. Handley (84) has recorded two cases of pineal tumour, both of which were characterized by accesses of mental excitement that led to their admission to a mental hospital, and it is probable that transient and recurrent blocking of the aqueduct and sudden marked rise in intracranial tension determined these symptoms. Just as the frequency of drowsiness in tumours as widely different in situation as the third ventricle and the corpus callosum should make us cautious in drawing inferences as to localization of function, so the case of the mental states seen in frontal lobe tumours should not make us blind to the fact that comparable abnormal mental

states are from time to time found in association with tumours remote from the frontal lobes. Clinically, however, it is certainly characteristic of tumours in this region that altered mental states more commonly usher in the picture than is the case with tumours elsewhere within the skull.

Pari passu with the evolution of this mental symptom-complex is the slow development of general pressure signs, of which headache is said to be the earliest, and of neighbourhood signs as the tumour by invasion or by compression affects the function of surrounding regions of the brain. These include loss of the crossed abdominal reflexes and slight paresis of the lower face. Later, definite crossed hemiparesis with the appropriate reflex alterations may appear. Among other symptoms recorded in frontal lobe tumours are a fine tremor of the extended homolateral hand and arm, nose rubbing (which has been attributed to irritation of the olfactory bulbs), while in left-sided tumours aphasia or apraxic disorders may appear. Occasionally, when the tumour lies far back towards the motor cortex, and also near the midline, the phenomenon of forced grasping (Wilson and Walshe (162), Adie and Critchley (1)) and a loss of optic nystagmus towards the opposite side (Fox and Holmes (66)) may be observed.

A characteristic symptom-complex is associated with meningioma of the olfactory groove. It includes the signs and symptoms already noted, with the addition of unilateral or bilateral anosmia (from compression of the olfactory bulbs) and of homolateral loss of vision from compression of one optic nerve. The optic disk on this side is normal in appearance at first, later developing a primary atrophy, while in the crossed eye is the papilloedema of raised intracranial pressure (Kennedy (99), Cushing (34)).

In respect of the mental disorders already enumerated, tumours of the corpus callosum (Guillain (82), Ironside and Guttmacher (97), Alpers and Grant (3)) resemble those of the frontal lobe, and in both instances these disorders may usher in the clinical picture, signs of raised intracranial pressure coming later. However, from the median situation of callosal tumours, and from the fact that they may arise in any part of this structure from genu to splenium, neighbourhood symptoms seldom seen in association with frontal tumours develop. These are (i) bilateral signs of pyramidal involvement, usually a hemiparesis on one side with increased tendon-jerks and an extensor plantar response on the other; (ii) the occasional presence of apraxia; (iii) generalized epileptiform convulsions, both as initial and as later symptoms; (iv) the frequent presence of xanthochromia in the cerebrospinal fluid (Guillain, Ironside, and Guttmacher); and (v) marked drowsiness (Gullain, Ironside, and Guttmacher, Alpers and Grant). The last-named symptom, as has been mentioned, is commonly seen in the case of third ventricle tumours. It may be added that in callosal tumours there is sometimes seen a profound immobility and hebetude which resembles, and yet differs from, drowsiness.

(e) *Tumours of the temporal and occipital lobes.* These may be briefly dealt with together, since tumours originating in the latter lobe frequently

invade the former, and the passage of the geniculo-calcarine visual fibres through both lobes renders an homonymous hemianopia a common localizing sign in both cases. Cushing (30) first drew attention to the frequent occurrence of homonymous hemianopia, quadrantic or complete, in temporal lobe tumours, and has fully discussed and illustrated the anatomical relationships underlying this phenomenon. Statistics (Kennedy (99), Cushing (30), Kolodny (102)) vary as to the frequency of this defect in the visual field, and it is clear that a tumour confined to the anterior or inferior portion of the lobe may leave the visual pathway intact, and so long as it is borne in mind that hemianopia does not necessarily indicate the occipital lobe as the seat of tumour, no good purpose is served by the citation of figures.

Further, subjective visual phenomena may accompany tumours in either lobe, in association with normal or hemianopic visual fields. In the case of occipital tumour, transient, unformed, visual sensations of a crude nature may occur as the aura of a generalized convulsion, or may occur without a subsequent epileptiform fit. In the case of temporal lobe tumours, complex visual hallucinations may accompany the characteristic uncinate fit, first described by Hughlings Jackson under the name of the 'dreamy state'. Various writers have described the elaborate scenes recorded by the subjects of such fits, with which olfactory or gustatory sensations may be associated.

Generalized epileptiform fits, presenting no localizing features, are common accompaniments of fits in both lobes, and in such circumstances may, as already emphasized, constitute the initial indication of the presence of tumour.

The neighbourhood signs show wider points of distinction in each case. Crossed hemiparesis is a common phenomenon at some stage in the development of a temporal lobe tumour, though in many cases a mild facial paresis of central type may be the only indication of compression of the cortico-spinal path. In these circumstances the symptom may arise from pressure exerted upwards against the lower portion of the excitable motor cortex, while on the other hand, an involvement of the crossed limbs, also, has been explained as due to pressure exerted mesially against the cerebral peduncle. The probable origin of the homolateral hemiparesis occasionally seen in temporal lobe tumour has already been considered in connexion with false localizing signs. Motor symptoms of this order are not common in occipital lobe tumours.

Occasionally in large temporal lobe tumours, as also in occipital lobe tumours, a relative hemianaesthesia may be found. According to Allen (2) this tends in the latter case to conform to the type of sensory change associated with lesions above the level of the thalamus. In the case of temporal lobe tumours such a distinction does not commonly obtain, all forms of sensation tend to be involved, and in a few cases pain and qualitative sensory changes resembling those associated with lesions of the thalamus may be observed.

As in all tumours that give rise to considerable rise of intracranial pressure, progressive mental blunting may develop in temporal tumours. These symptoms approximate in type to those described in connexion with the frontal

lobe, but differ from them in that they are commonly an initial accompaniment of frontal lobe tumours, but a relatively late one of temporal lobe tumours. In left-sided tumours a degree of visual word blindness may accompany occipital lobe tumours, and disturbances of auditory word memory with corresponding defects of expression tumours of the temporal lobe.

It remains to be said that certain cases of temporal lobe tumour, especially of the right hemisphere, may present no localizing signs whatever until the terminal stages of the condition have arrived.

(e) *Tumours of the cerebellum.* Reference has already been made to the symptomatology of tumours of the cerebello-pontile angle and to those arising within the fourth ventricle. The cerebellar symptom-complex has for many years been the subject of very numerous clinical studies, and no detailed account is necessary here, but for a brief summary of recent views on the subject the reader may be referred to a discussion on the cerebellar symptom-complex held by a joint meeting of the American Neurological Association and the Neurological Section of the Royal Society of Medicine and reported in *Brain* (Volume 50).

(f) *Metastatic carcinoma: a metastatic syndrome.* We have seen that in secondary carcinoma the lesion may consist of a single or of multiple nodules within the brain, or of a diffuse carcinomatous infiltration of the pia-arachnoid, or of both combined.

It has been suggested (Globus and Selinsky (74), Ferguson and Rees (61)) that there may be a recognizable 'cerebral metastatic syndrome' by which the secondary nature of the growth in a case of intracranial tumour may be detected clinically. Winkelmann and Eckel (163), on the other hand, doubt the existence of such a syndrome.

However, from the cases of Saenger (136), Seifert (143), Scholz (138), Lilienfeld and Benda (106), Stadelmann (147), Schwarz and Bertels (142), and of the more recent papers already cited, it seems possible to construct a clinical picture that is highly characteristic of most cases of metastatic growths of the brain and meninges. The clinical course frequently opens somewhat abruptly with such mental symptoms as apathy, drowsiness, accesses of psychomotor excitement alternating with stupor and leading to a terminal coma. Associated with these are signs and symptoms resembling those of tuberculous meningitis; generalized or focal convulsions, rigidity of the neck and Kernig's sign, occipital headache, vomiting, cranial nerve palsies, incontinence or retention of urine, and also—in the complete syndrome—papilloedema and signs of focal lesions within the brain. Rapid wasting and emaciation, and sometimes an irregular pyrexia, complete the picture. Schwarz and Bertels record the finding of free carcinoma cells in the cerebrospinal fluid on lumbar puncture.

Those who have sought to establish the occurrence of a metastatic syndrome appear to regard the multiplicity of the tumour nodules as responsible, and do not associate it with carcinomatous infiltration of the pia-arachnoid. Indeed, this lesion seems to have been observed fortuitously, and in most of the cases

of Cornwall, Globus and Selinsky, Fergusson and Rees, the meninges were not submitted to microscopic examination. Yet not only is it inherently probable that the meningeal involvement is the cause of those clinical features peculiar to secondary carcinoma of the brain, but, further, the syndrome has been present in cases in which meningeal carcinomatosis was alone present and tumour nodules within the brain were absent.

It may be suggested, therefore, that there are two components in the metastatic syndrome, one due to tumours within the brain, the other to malignant infiltration of the pia-arachnoid. A review of the clinical history of most cases of secondary carcinoma of the brain suggests the presence of meningeal involvement. In its absence it is probable that metastatic growths of the brain are clinically unrecognizable.

V. Diagnosis.

The clinical phenomena by which a diagnosis may be made have already been described, and it remains to consider briefly some supplementary methods of investigation. These are radiography and its applications: ventriculography and encephalography, the use of hyoscine for the elicitation of localizing signs, and the examination of the skull.

(i) *The Use of Hyoscine for the Elicitation of Localizing Signs.*

In the course of some observations upon the appearance of the Babinski type of plantar response in certain toxic states, Elliott and Walshe (58) found that a hypodermic injection of hyoscine hydrobromide in doses of from gr. 1/150 to gr. 1/100 sometimes caused a conversion of the normal plantar response to one of Babinski type: as, for example, in certain cases of post-encephalitic Parkinsonism. Lemos had previously made a similar observation (104). They found also that in a number of cases of intracranial tumour presenting no localizing signs, such an injection was followed by the temporary appearance of abnormal physical signs not previously present. Such, for example, as an extensor plantar response, or a facial paresis on one side. They cited one such case in the paper referred to in which such signs were later found to conform to the situation in which a small glioma was revealed at autopsy.

In a number of subsequent observations, this experience has been repeated. No untoward effects have ever been seen to follow such an injection, which is thus not only easily performed, and free from discomfort to the patient, but is perfectly safe. Like all other diagnostic procedures, this is not invariably of use, but its extended employment is indicated.

(ii) *Diagnostic Applications of Radiography.*

The radiography of the skull in intracranial tumour found its first application in the detection of those deformities of the sella turcica resulting from pituitary and supra-pituitary tumours. But with the recognition of the fact that a meningioma may invade the skull, that certain varieties of tumour may contain calcareous deposits, and that raised intracranial pressure may give rise to atrophic changes in the bones of the skull, the employment of radiography has become part of the routine investigation of every case of intracranial tumour (Sosman and Putnam (144)).

Further, Dandy (44) has introduced the method of air injection into the ventricles and subarachnoid space, thus rendering these visible in the radiogram. These are the procedures of ventriculography and encephalography.

(a) *Radiography.* An essential preliminary to the assessment of abnormalities in radiograms of the skull is an intimate acquaintance with the wide range of normal variations, and numerous errors of interpretation have arisen from absence of this elementary knowledge. From middle age onwards, calcareous deposits may be present in the pineal body, the choroid plexuses, and the falx cerebri. Large Pacchionian granulations may erode the bone and produce visible irregularities in the profile of the calvarium, and finally, there is a wide range of variation in the size and number of the bony channels in which the diploic vessels run (Jefferson and Stewart (98)). Careful study of the numerous clinical records of cases of intracranial tumour reveals that not infrequently apparently abnormal appearances are seen in radiograms of the skull, which the event proves to have stood in no relation either to the presence or the localization of the tumour. Such discordant findings rarely obtain comment from writers, though relevant findings are invariably stressed. Thus the frequency with which radiograms of the skull are either definitely misleading, or incapable of any interpretation, tends to be overlooked (Cushing (28)).

The alterations in the outline of the sella turcica from tumours of the pituitary region have already been enumerated. Hypophyseal duct tumours, gliomata, and meningiomata may contain calcified material, which in a stereoscopic radiogram betray their situation. The calvarium overlying a meningioma sometimes shows irregularities of profile and density when the bone is invaded, while the surrounding bone may show dilated diploic channels.

As a result of long-standing rise of intracranial pressure, diffuse or localized thinning of the overlying bone may ensue, producing the mottled appearance known as convolutional thinning. Similarly, there may be widening and shallowing of the sella and—in children—separation of the sutures. Finally, in cases of auditory nerve tumour there may be dilatation of the internal auditory meatus that appropriate radiography may reveal (Stenvers (148)).

(b) *Ventriculography.* Any deformity of the ventricular cavities produced by a tumour becomes visible when these have been filled with air by direct injection.

(c) *Encephalography.* Air injected into the spinal sub-arachnoid space, after lumbar puncture and the withdrawal of fluid, ascends and fills the ventricles and the cerebral sub-arachnoid space. Any obliteration of the latter, or any flattening or deformity of the cerebral convolutions, may thus be rendered visible in a radiogram.

In both these procedures, it is essential that perfect filling of the cavities should be obtained if misleading appearances are not to be produced. Neither method is free from danger, or from gross discomfort to the subject. Fatalities have followed ventriculography (Grant (78), Cairns (19)) and a sound balance of opinion as to the value and scope of these diagnostic measures has yet to be reached.

However, after all allowance has been made for the enthusiasm that commonly greets some new diagnostic device, especially one involving surgical intervention and the use of apparatus, it seems clear that both methods have a definite place in investigation, more especially when a localization cannot be made by ordinary clinical means. The general body of opinion suggests that air injections are inadvisable (i) when there is a severe degree of intracranial hypertension, and (ii) unless the surgeon who carries them out is prepared to proceed at once to operation should a sudden rise in pressure follow the injection, as sometimes happens.

(iii) *Examination of Scalp and Skull.*

After the head has been shaved, local or diffuse venous dilatation may be seen. In young children, separation of the sutures and a 'cracked pot sound' on percussion may be present. Invasion of the bone by endothelioma produces visible bossing of the skull. This may be nodular and not prominent, or in the case of frontally situated tumours a large hemispherical boss may be seen. These prominences are hard, generally relatively painless to pressure, and the skin moves freely over them. They are almost invariably found on some part of the frontal bone.

VI. Treatment.

It is not yet possible to assess the part that X-ray or radium therapy may take in the treatment of intracranial tumours, especially in that of the gliomata, and for the present such possibilities of relief and cure as there are depend upon surgical intervention. It is not here practicable to do more than summarize the general principles governing such intervention, and to state what may reasonably be expected from it.

In the case of unlocalized or inaccessible growths, all that is possible is decompressive craniectomy for the relief of headache, the saving of useful vision, or the prolongation of life until localizing signs may appear and render more radical measures practicable. When such signs are present and indicate accessibility of the tumour, it becomes of importance to form some judgement as to the pathological nature of the latter.

From what has already been said of the behaviour of the different varieties of glioma, it is clear that interference with a rapidly growing glioblastoma may be followed by spreading oedema of the brain and early death. Again, Cushing's experiences suggest the futility of attempts to extirpate a medullo-blastoma. On the other hand, the cystic astrocytoma of the cerebellum is eminently favourable for extirpation, and if the tumour nodule in the cyst wall be removed the prognosis as to survival and as to restoration of useful motor function is excellent. Similarly, the clinical differentiation of pituitary adenoma from hypophyseal duct tumour is important, as the former is frequently, but the latter rarely, amenable to surgical measures. Further, with some knowledge as to the variety of growth he may expect to encounter, the surgeon is most favourably placed to take in advance such special steps to deal with this as experience may dictate. Thus, in the case of a suspected meningioma the possible attachment of the growth to the bone and an increased vascularity of the latter call for special measures. Therefore, in deciding as to the expediency of operation and as to the nature of the procedure to be adopted, an accurate estimate of the nature as well as of the situation of the tumour is desirable.

In assessing the results of the surgery of intracranial tumour, it is desirable to have some precise criterion of successful treatment. In the case of the infiltrating tumours of the brain, the gliomata, it is a common practice to record results in terms of 'survival period'. It is uncommon to find embodied in such records any adequate post-operative neurological details, and such euphemisms as 'the patient did well' are the usual substitute for this. Now that 'amputation' of whole lobes (128), and even of complete hemispheres, is becoming more common in the endeavour completely to extirpate a glioma, it is clear that distressing residual disabilities must ensue in many cases, and these may not unreasonably be balanced against the prolongation of life obtained by such extensive mutilations of the brain. In this matter every one must strike his own balance, and in doing so will consider the quality of the existence thus prolonged. This may be purely vegetative.

On the other hand, in the case of the encapsuled tumours of the meninges, meningioma and auditory nerve tumour, and of the pituitary adenomata, successful extirpation, with the restoration of useful function, may reasonably be expected in many instances together with freedom from recurrence. As has been indicated, a comparable measure of success may attend the surgery of the cystic astrocytoma of the cerebellum.

X-ray and radium therapy. As far as is at present apparent, only the pituitary adenomata and some varieties of glioma are influenced by these forms of radiation. Dott and Bailey (56) report favourable results from deep X-ray therapy, and give technical details of their procedure. On the other hand, they found that the implantation of radium seeds in the tumour was of no avail (1925).

Cushing advocates X-ray therapy after subtentorial decompression as the

most effective treatment for medulloblastoma. Desjardins (53) reported his experience of X-ray therapy on a large series of tumour cases at the Mayo Clinic. At this clinic radiotherapy is always combined with surgical measures, so that the part played by the former in such amelioration as was noted is difficult to estimate. The reader may be referred to this paper for the best technical account of this form of treatment.

The general experience seems to be that the rapidly growing and malignant varieties of glioma are uninfluenced by any form of radiation.

Of the results of radium therapy it is not yet possible to speak with any certainty.

The temporary relief of increased intracranial pressure by hypertonic solutions. Weed and McKibben's observation that the brain volume and cerebrospinal fluid pressure may be reduced by the intravenous injection of hypertonic salt solution has been applied in cases of raised pressure from intracranial tumour (Foley (65), Foley and Putnam (64), Grant (77)). There are several circumstances in which it may be desirable to lower the intracranial pressure and to reduce the volume of the brain; for example, to relieve pressure headache, to avert impending death, and to restore to consciousness a stuporose patient in order that an adequate clinical examination may be made, or as a preliminary to operation. Intravenous, oral and rectal, administrations of hypertonic solutions have been used. When a rapid effect is desired the slow intravenous injection of from 50 to 75 c.c. of a 15 per cent. solution of sodium chloride, or 60 c.c. of a 50 per cent. glucose solution may be made. In other circumstances, the rectal administration of from 2 to 3 ounces of magnesium sulphate in from 5 to 8 ounces of water will suffice. This procedure may be repeated as necessary. By this means great relief from headache may be obtained, and a cerebral hernia may be seen to diminish markedly in size and tension. The most striking results are obtained when there is obstruction to the flow of cerebrospinal fluid, but when pressure is mainly due to increased brain volume from the presence of a large tumour, less benefit is obtained.

Medicinal treatment. Apart from purely symptomatic measures, drugs have no place in the treatment of any variety of intracranial new growth, the granulomata not being included in this generalization. For the latter, the remedies employed for the responsible infections when they occur elsewhere in the body are employed, though in the case of syphilis the possibility that operative intervention may be called for has already been mentioned.

In the case of pituitary adenoma, organotherapy has so far proved ineffective, though there is some evidence that the administration of thyroid extract may temporarily retard the development of an adenoma—if we may take a recession of the temporal visual field defect as an indication of this.

Mercurial inunction combined with the administration of potassium iodide has the sanction of long usage for intracranial tumour, but the evidence of their efficacy is meagre.

VII. Conclusion.

The pathological range of new growths that may arise in the brain and its membranes is a wide one, and it is probable that the time is already past when the subject can be fruitfully dealt with as a whole. Each variety of tumour has its own characteristic life history, its peculiar age of incidence, and its favourite site of origin. Each demands a special surgical technique in its treatment. Clinically, also, there is a comparably wide range of symptom-complexes and of clinical histories. These vary between such widely separated extremes as that of acromegaly to that of an auditory nerve tumour; from a short and rapidly fatal illness to a long drawn-out affection of which for years an occasional fit may be the sole expression. The subject is no more a homogeneous one than is that of abdominal tumours, and it is probable that the future writer of a general review will have to confine his attention either to a single pathological group of tumours, or to some characteristic localization syndrome. From the brief account that has been given of the variation in the structure and behaviour of the tumours comprising the glioma group it may be suggested that it will be along the former line that the most adequate exposition will be possible.

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PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

TWENTY-FOURTH ANNUAL GENERAL MEETING

THE TWENTY-FOURTH ANNUAL GENERAL MEETING was held in London on Friday and Saturday, June 6 and 7, 1930, in the House of the Royal Society of Medicine. The Attendance Book for the Meeting was signed by 227 members. The proceedings began at 10 a.m.

The President, Sir Humphry Rolleston, was in the Chair.

The Minutes of the last Annual Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

Election of Officers.

President. Sir William Hale-White was elected President for 1930–31. On his election he took the Chair and expressed the thanks of the Association to the retiring President for his services during the past year.

Honorary Member. Sir John Rose Bradford was elected an Honorary Member. The President referred to his long and valuable services as an Editor of the *Quarterly Journal of Medicine.*

Election of Officers, members of the Executive Committee, Extra-ordinary members, and Ordinary members followed.

Treasurer. Dr. H. Morley Fletcher.

Secretary. Dr. H. Letheby Tidy.

Members for England:

Dr. W. Langdon Brown.
Dr. Carey Coombs.
Dr. Gordon M. Holmes.
Dr. A. E. Naish.
Professor A. Ramsbottom.
Dr. R. A. Young.

Members for Scotland:

Dr. A. Greig Anderson.
Dr. R. A. Fleming.
Dr. Ivy Mackenzie.

Members for Ireland:

Sir Thomas Houston.
Professor T. G. Moorhead.
Professor V. M. Synge.

As Extra-ordinary members:

Dr. John Fawcett.
Dr. G. L. Gulland.
Sir Robert Philip.
Dr. G. A. Sutherland.
Dr. J. O. Symes.
Dr. J. Aldren Wright.

ASSOCIATION OF PHYSICIANS

Ordinary members:

Frederick M. B. Allen, M.D., Assistant Physician, Hospital for Sick Children, Belfast.

Ernest Noble Chamberlain, M.D., Assistant Physician, Royal Southern Hospital, Liverpool.

Leslie B. Cole, M.D., Assistant Physician, Addenbrooke's Hospital, Cambridge.

Arthur Henry Douthwaite, M.D., Assistant Physician, Guy's Hospital.

Fergus Robert Ferguson, M.D., Assistant Physician, Royal Infirmary, Manchester.

Stanley G. Graham, M.D., Assistant Physician, Royal Hospital for Sick Children, Glasgow.

Reginald Hilton, M.B., Assistant Physician, St. Bartholomew's Hospital.

Joseph Tagart Lewis, M.D., Assistant Physician, Royal Victoria Hospital, Belfast.

Robert Platt, M.D., Medical Registrar, Royal Infirmary, Sheffield.

James Maclure Smellie, M.D., Assistant Physician, General Infirmary, Birmingham.

William R. Snodgrass, M.B., Assistant Physician, Western Infirmary, Glasgow.

John Spears, M.D., Visiting Physician, Adelaide Hospital, Dublin.

Leslie John Witts, M.D., Assistant Physician, Guy's Hospital.

Frederick Hugh Young, M.D., Assistant Physician, Charing Cross Hospital.

Presentation of Treasurer's Accounts. Dr. Morley Fletcher (Treasurer) presented the Annual Accounts, which were adopted. They showed a balance of £237 15*s.* 2*d.*

Annual General Meeting in 1931. A letter was read from Dr. A. J. Hall inviting the Association to meet in Sheffield in 1931. The invitation was cordially accepted.

Quarterly Journal of Medicine. Dr. Morley Fletcher, on behalf of the Executive Committee, recommended the appointment of Dr. J. W. McNee as Editor of the *Journal* on the nomination of the Board of Editors in place of Dr. Hurst, who had resigned. This was agreed to unanimously.

Harvey Memorial Appeal. On the motion of the President, it was agreed to contribute the sum of 15 guineas from the funds of the Association.

SCIENTIFIC BUSINESS.

Friday Morning Session.

1. Dr. A. F. Hurst and Dr. F. A. Knott (introduced) on *Intestinal Carbohydrate Dyspepsia.* Acute infections of the alimentary tract are frequently followed by a permanent diminution in the secretion of the small intestine, that of the stomach and colon remaining unaffected. This leads to deficient digestion of starch, as the diastase of the succus entericus is much more important than the ptyalin of the saliva and the amylopsin of the pancreatic juice. In this condition the starch contained in cellulose envelopes reaches the caecum, where it is digested by the coecal diastase. The bacteria of the colon break up the sugar formed in the colon

when the small intestine digestion is incomplete, and the excess of gas produced gives rise to the symptoms of 'carbohydrate intestinal dyspepsia'. The condition can be completely relieved by avoiding potatoes and other root vegetables and by taking vegetable diastase, which is not decomposed by gastric juice, in order to compensate for the deficient diastase of the succus entericus. The stools in carbohydrate intestinal digestion contain excess of starch granules and excess of enterococci, and they undergo fermentation with production of excess of gas on incubation.

2. Dr. Leonard Findlay gave a communication on *Pulmonary Lesions in Rheumatism.* The cellular exudate in the pleural effusion met with in examples of rheumatic pericarditis and carditis during childhood reveals many endothelial cells in addition to lymphocytes and polymorphs. This is the picture which is characteristic of the passive pleural exudate. On this ground it is concluded that the pleural effusion in rheumatic pericarditis is passive in nature and the result of cardiac failure.

From a study of a series of 25 cases the following conclusions seemed justified:

(1) The rheumatic poison shows no predilection for the pleura or the lung.

(2) The most frequent pulmonary complication in rheumatism in childhood is pleural effusion.

(3) This occurs most frequently with pericarditis.

(4) This pleural effusion is of the nature of a transudate.

(5) The pleural effusion occurs more frequently at the left base and should always be suspected when the percussion note is impaired at the left base even if the breath sounds are intensely tubular in character and râles are present.

(6) Pulmonary lesions in rheumatism are of the nature of (*a*) an intercurrent disease (lobar pneumonia) or (*b*) a terminal hypostatic or broncho-pneumonia complicating cardiac disease.

This communication was discussed by many members, including Drs. Abrahamson, Poynton, Naish, Coombs, and Sir Charlton Briscoe.

Dr. Findlay replied.

3. Sir Thomas Horder gave a communication on *Septic Endocarditis.* (*Twenty years after.*) Little of significance has been added to our knowledge since 1908.

(1) The clinical picture has been confirmed and elaborated. The café-au-lait complexion is of frequent occurrence. Clubbed fingers have been studied by Cotton. Streaks and splashes of minute haemorrhage under the nails have been described by Horder. Hale-White has stressed the importance of routine urine examinations for red blood-cells. In the blood counts the most common finding as regards the white cells is a figure a little above or a little below the normal. Peck has found an absolute in large mononuclear cells.

(2) The war group of cases was mainly aortic in distribution, and perhaps the element of prolonged strain entered into the aetiology. The existence of apyrexial periods, sometimes prolonged, was a new feature. In many of the cases there was no evidence of previous valve damage.

(3) Relapsing cases have been noted by Libman and others.

(4) In the bacteriology of the disease the preponderance of streptococcal infections has been amply confirmed.

(5) Serological studies show no specificity in the group as a whole, as judged by complement-fixation.

(6) Morbid anatomy. The influence of small congenital defects in the aortic cusps and neighbourhood has been demonstrated by Lewis and others.

(7) In therapeutics it is generally agreed that serum and antigen therapy not infrequently hastens the course of the disease.

Drs. Abrahamson, Cowan, Stacey Wilson, Poynton, and Ivor Davies took part in the discussion.

Dr. L. ABRAHAMSON brought forward three cases in which subacute endocarditis had followed the removal of septic foci. One patient, a man aged 39, had suffered from mitral regurgitation for 10 to 12 years. From this he had experienced no disability. Eleven teeth were extracted under local anaesthesia in January 1925. Shortly afterwards he experienced stiffness of his calves and thighs, and petechiae on his fingers. On April 25, 1925, he developed a stroke with a right-sided hemiplegia. This was followed by mild remittent pyrexia, crops of tender nodules and petechiae. Blood-culture yielded a streptococcus viridans. On September 20, 1925, he developed a second stroke which proved fatal.

4. Professor W. T. RITCHIE discussed *The Action of Adenosine upon the Human Heart.* No recognizable effect followed subcutaneous injection: after intravenous injection there was transient retardation of the heart's rate and impairment of conduction from auricle to ventricle, with consequent partial heart-block. Auricular fibrillation persisted, even after the amount of adenosine that had been injected was so large as to produce undesirable effects.

5. Dr. D. EVAN BEDFORD and Dr. JOHN PARKINSON recorded observations on the *Topographical Anatomy and Radiology of Mitral Stenosis.* Drawings and photographs were made of the heart *in situ* in the cadaver in cases of mitral stenosis, and these were correlated with radiograms of the heart in mitral stenosis. Normally the left auricle is median in position, but in mitral stenosis, owing to rotation of the heart, it tends to enlarge towards the right and never to the left. The left auricular appendix is displaced backwards and is often invisible from the front. The enlarged 'middle arc' on the left in radiograms of mitral stenosis is due mainly or entirely to the enlarged conus arteriosus of the right ventricle and pulmonary artery. Enlargement of the left auricle to the right can be recognized in radiograms in about 30 per cent. of adult cases. It may be visible through the right auricle, may project beyond the right auricle below the right lung root, or may form the whole right border of the heart in cases of aneurysmal dilatation.

Radiograms, anatomical drawings, and photographs were shown.

Dr. Wardrop Griffith and Dr. Langdon Brown discussed these observations.

6. Dr. M. CAMPBELL and Dr. J. W. SHACKLE (introduced) on *The Etiology of Disease of the Aortic Valves.* In nearly 300 consecutive cases with disease of the aortic valves, this was due to rheumatism in 200, to syphilis in 52, to atheroma in 22, and to all other causes in 22 more.

Of the rheumatic cases, three of each six had aortic incompetence and mitral stenosis, one had these and aortic stenosis as well, one aortic stenosis and incompetence, and one aortic incompetence alone. Among those without mitral disease, there were two men for each woman; among those with mitral disease, three women for each two men. Pure aortic stenosis was uncommon, and as judged by the pulse pressure it was unimportant compared with the incompetence, even when the signs were obvious.

Among the syphilitic cases there were three men for each woman; nearly four-fifths were between 40 and 60. Aortic stenosis was rare.

Nearly all the atheromatous cases were men between 50 and 80. Generally aortic stenosis was the more important lesion, and free regurgitation was less common.

2–3 p.m. *Friday and Saturday.*

A Demonstration of Clinical cases was given in the rooms of the Royal Society of Medicine and the College of Nursing.

An extensive Historical Exhibition was given by the Wellcome Historical Medical Museum.

The Wellcome Museum of Medical Science exhibited a complete section illustrating Malaria.

An Exhibition of Pathological Specimens and Radiographs were also on view.

The Library of the Royal Society of Medicine exhibited some rare editions.

3 p.m. *Afternoon Session.*

1. Dr. STANLEY DAVIDSON on *The Blood-Picture in Certain Cases of Acute Lymphadenoma.* He had seen several cases of Hodgkin's disease in which the actual cause of death was an extremely severe anaemia, closely resembling pernicious anaemia. The anaemia did not respond to liver therapy. In addition a marked hyperplastic reaction of the bone-marrow was evidenced by high reticulocyte percentage counts (30–50 per cent. in one case) over a long period, without any increase in the blood count. This feature clearly distinguished the condition from idiopathic pernicious anaemia, and were more in keeping with acholuric jaundice. The diagnosis of acute Hodgkin's disease was made during life, and was confirmed *post mortem* by the naked-eye and microscopic appearances. It was suggested that in certain acute cases of Hodgkin's disease in which the abdominal organs, particularly the spleen, are affected, marked blood-destruction occurs which results in an anaemia of a haemoclastic megalocytic type.

This communication was discussed by Drs. Gow, W. Hunter, Hurst, and Sir Humphry Rolleston.

2. Dr. A. GOODALL referred to the efficacy of the oral administration of liver, stomach, and kidney, and of transfusion of blood in 'Pernicious Anaemia'. He suggested that pernicious anaemia is due to failure on the part of the bone-marrow to elaborate normoblasts and normocytes from the more primitive megaloblasts. This failure can be met by a substance, probably a hormone, elaborated in the stomach, passed through the liver into the general circulation, and filtered off in the kidneys.

Of all methods of treating pernicious anaemia, transfusion was the most efficient. The criterion of success was a satisfactory reticulocyte reaction. When this occurred, treatment by liver or stomach would complete the cure.

3. Dr. T. EAST described *Two Cases of Pernicious Anaemia treated with Ventriculin or Extract of Hog's Stomach.* They had both failed to respond to liver in ordinary or extract form. On being given ventriculin the blood-picture in both instances was restored to normal in a few weeks. A third case was also mentioned, a young man who had a chlorotic type of anaemia. He had not benefited by iron, but had shown a considerable increase in the haemoglobin on ventriculin.

Similar cases were referred to by Drs. Hurst, S. Davidson, A. E. Russell, Veal, W. Hunter, and Goodall.

4. Dr. J. L. BIRLEY reported a *Case of Bilateral Adrenal Tumours associated with Eosinophilia.* The patient, a male, aged 29, was admitted to hospital on 26.12.29 with a six months' history of upper abdominal pain, and a one month's history of increasing dyspnoea and oedema of the feet. The superficial lymph-glands were moderately enlarged, the liver greatly enlarged and prominent, the spleen just palpable, the blood-pressure low (105/70 m.m. Hg.). Blood W.R. strongly positive; macular rash and no history of syphilis. Blood-count—R.C. 4,570,000; Hb. 74 per cent.; C. I. 0·82; W.C. 40,200. Eosinophils 90·5 per cent. No myelocytes. Two days before death (16.1.30) after a febrile illness characterized by increasing dyspnoea, oedema of legs, ascites and hydrothorax, blood-count showed R.C. 3,930,000; Hb. 76 per cent.; C.I. 0·97; W.C. 14,540. Eosinophils 70·6 per cent. No myelocytes. All the eosinophils were of the mature type.

Autopsy: Enormous tumours (wt. 47 and 43 ozs.) of both adrenals. Histologically ? Lymphosarcoma (no nerve fibrils). Moderate enlargement of all lymphatic glands with patchy increase of reticular tissue, small giant cells, excess of eosinophils, and areas of necrosis. Similar changes were present in the spleen and intestinal wall. Bone-marrow showed general erythro- and leucoblastic activity, with predominance of eosinophilic myelocytes and polymorphs.

The condition was regarded as being malignant (lymphosarcomatosis), or semi-malignant (lymphogranulomatosis).

5. Dr. GEORGE GRAHAM and R. S. JOHNSON (introduced) on *Anaemia and Dysphagia.* They described the clinical appearance of six patients, in whom a secondary anaemia was associated with dysphagia, sore tongue, and cracked lips. These patients were typical of the syndrome originally described by Paterson, Brown-Kelly, Plummer, Vinson, Moerch, and Conner, except that in one patient no dysphagia was present.

Achlorhydria was present in all six patients. In five out of six fragility of the red cells was increased as haemolysis occurred at 0·45 or 0·5 per cent. sodium chloride solution.

This communication was discussed by Drs. Hurst, Gillespie, and Abrahams.

6. Dr. J. A. RYLE reported his observations on five cases of wandering thrombophlebitis—*Thrombo-phlebitis Migrans*—in four of which there were visceral thromboses. In 1928 Moorhead and Abrahamson had described for the first time cases complicated by pulmonary, abdominal, and cardiac thromboses. He had been able to collect eight examples of pulmonary thrombosis, four of abdominal thrombosis, three probable examples of cardiac and two of cerebral thrombosis. In one of his own cases there were symptoms of abdominal and bilateral pulmonary thromboses without any superficial lesion. In three of these cases there was evidence of focal streptococcic infection. The visceral symptoms might cause great anxiety. Nevertheless, the prognosis is favourable.

Drs. Moorhead, Edgecomb, and Tidy discussed these cases.

7. Dr. H. GARDINER HILL described a case of *Chlorotic Anaemia in a Male.* A boy of 17½, mentally and physically backward, presented a picture typical of the chlorosis of adolescent females. Stained films showed pessary corpuscles, anisocytosis, and poikilocytosis, and the blood-count after three month's treatment with iron changed from red cells 5,000,000; Hb. 38 per cent.; C.I. 0·4; to red cells 4,920,000; Hb. 98 per cent.; C.I. 1. Interesting features were a history of vegetarianism, and a delay in sex-development characteristic of eunuchoidism.

The *Annual Dinner* was held at 7.45 for 8 p.m. at the May Fair Hotel. Sir William Hale-White was in the Chair. The official guests were the Rt. Hon. Lord Justice Macmillan, Sir John Rose Bradford (President of the Royal College of Physicians), Lord Moynihan (President of the Royal College of Surgeons), Lord Dawson (President of the Royal Society of Medicine). 161 members and guests were present.

Saturday 10 a.m. *Morning Session.*

1. Dr. DONALD HUNTER gave an important communication on *Clinical Hyperparathyroidism.* By means of a cinematograph film the effects of total thyro-parathyroidectomy in dogs and cats were demonstrated. The tetany was relieved by injections of parathyroid extract (Collip). The prolonged use of such injections in man was shown to raise the serum calcium (Collip), and to increase the output of calcium in the urine (Hunter and Aub). This calcium comes from the bones. After three years search amongst cases of osteitis fibrosa, a patient with generalized osteitis fibrosa (von Recklinghausen) was found in whom the serum calcium was 16·7 mg. per 100 c.c. and the calcium output in the urine six times the normal. No swelling was palpable in the neck, but on exploration a parathyroid tumour was discovered and removed (Mr. A. J. Walton). The pains in the bones ceased, the calcium metabolism was promptly restored to normal, and the X-ray shadows of the bones became more dense. This was the tenth case published where a parathyroid tumour had been removed in generalized osteitis fibrosa. The first case was operated upon in 1925 by Mandl of Vienna; the other cases had occurred in Germany, Holland, and the United States of America. In focal osteitis fibrosa evidence of hyperparathyroidism is lacking, and operation upon the neck is entirely unjustified even if many bones are affected.

2. Dr. DAVID CAMPBELL on *Parathyroid Tetany.* The problem presented was the treatment of a case of tetany following complete removal of the parathyroid glands during the operation of thyroidectomy. Eighteen hours after the operation the patient was in marked tetany. This was relieved by the intravenous injection of a 10 per cent. solution of calcium chloride, and the improvement was maintained for nearly 24 hours. The subcutaneous injection of 10 units of Collip's Parathormone thrice daily resulted in definite improvement of the symptoms of tetany without much rise in the calcium content of the blood-serum. Feeding with 2 litres of milk per day plus 100 c.c. of N/1 HCl resulted in a rise of blood-calcium to nearly normal, and a complete disappearance of the symptoms of tetany. Ultimately the best treatment was found to be (*a*) 2 litres of milk per day, (*b*) $CaCl_2$ 150 grains by the mouth, and (*c*) 100 c.c. of N/1 HCl per diem. This has kept the patient in apparent perfect health for months. A slight reduction in the calcium chloride or the acid leads to the signs of tetany reappearing.

3. Dr. C. F. HARRIS (introduced) on *Calcium and Phosphorus Metabolism in Tetany following Thyroidectomy.* The patient studied was a woman aged 20, who had had symptoms of tetany for sixteen months. The tetany was apparently due to parathyroid deficiency following thyroidectomy. The investigation involved giving the patient a known and constant amount of calcium and phosphorus in her food and measuring the output of these elements in her faeces and urine. At the same time observations on the amount of calcium and phosphorus in the blood-serum were made.

Observations were carried out over two periods, one of seventy days and the other ninety days. During the time that the patient still had symptoms of tetany, the level of the calcium in the serum fluctuated between 8 and 9 mg. per cent., a figure which seemed unusually high. The serum phosphorus remained constant at about 5 mg. per cent. While no drugs were given, the intake and output of calcium were approximately balanced and there was an apparent storing of phosphorus. The administration of extract of dried thyroid gland gave rise to definitely negative balance of calcium and diminished the positive balance of phosphorus. The tetany was relieved only when large doses of the extract, 9 grains a day, were given. At the same time the serum calcium rose above 10 mg. per cent.

A short period of treatment with 30 units a day of Collip's parathyroid extract was observed. Although this gave rise to a negative balance of both calcium and phosphorus, the serum calcium was not increased nor was the tetany relieved. During a period of treatment with 36,000 units of irradiated ergosterol daily over twenty-four days, the negative balance of calcium was considerably increased.

These three communications were discussed together by Drs. Parkes Weber, Findlay, and Ellis.

4. Dr. A. M. COOKE (introduced), under the title of *Observations on Alkalosis,* reported four cases in which severe symptoms had followed the treatment of gastric and duodenal ulcer by alkaline diet. Uncompensated alkalosis occurs in about 3 per cent. of patients treated with soluble alkalis. The chief clinical features are headache, backache, pains in the limbs, dry mouth, loss of appetite, vomiting, mental irritability, bloodshot eyes, and, in some cases, tetany. Convulsions, coma, and death have been recorded in a few instances. Biochemical investigations of the blood show a rise in pH, a marked rise in the CO_2 combining power of the plasma, in the non-protein nitrogen (due to an increase in the urea fraction) and in the inorganic phosphorus, associated with a profound depression of the chlorides. The urine is usually alkaline (but may occasionally be acid), contains albumin and casts, and, in severe cases, ketone bodies and lactic acid. The daily excretion of nitrogen, urea, and phosphorus is not markedly disturbed, but chloride excretion is almost absent. Owing to the rather vague symptoms of the condition and the lack of any pathognomic clinical signs, a careful watch should be kept on all cases treated with alkalis, and the diagnosis should be confirmed by chemical methods, of which the simplest and most usually accessible is estimation of the blood urea. Early diagnosis is important. Treatment consists in stopping alkalis, when recovery is usually rapid and complete. In the cases reported no residual renal damage was found.

Drs. Hurst, Findlay, Russell, and Ryle took part in the discussion which followed, and Dr. Cooke replied.

5. Professor F. R. Fraser discussed *The Results of Treatment of Exophthalmic Goitre.* A series of cases of toxic goitre were analysed. The patients had been in the hospital wards during 1920–25, and the results noted in 1930. The results of surgical and non-surgical methods of treatment were compared. The cases were further subdivided into those of primary and secondary Graves's Disease. Of the patients whose condition was severe enough to require their admission to hospital, surgical treatment is indicated in those with secondary Graves's Disease, and also in those with primary Graves's Disease who do not improve rapidly, or who for financial or other reasons cannot submit to satisfactory treatment and observation. In a number of younger patients with primary Graves's Disease, recovery takes place without surgical treatment.

6. Professor H. MacLean reported *Observations on Gastric Secretion and Alkaline Treatment.* He argued that the regulation of the normal acidity of the stomach is unconnected with regurgitation of alkaline contents from the duodenum. The regulation of gastric acidity is dependent upon an automatic mechanism; whenever the acidity reaches a certain strength this mechanism acts by virtue of the H-ion concentration, and inhibits the production of further acid. When 0·2 per cent. or so of hydrochloric acid is introduced into the stomach by a Rehfuss tube, no further acid is formed by the stomach, though large amounts of pepsin and sodium chloride are secreted. This inhibitory action of acid is brought about by the presence of acid in the duodenum, for the passage of acid by means of a tube into the viscus prevents stomach secretion of acid.

7. Dr. T. Izod Bennett, under the title of *Asthenic Achylia*, reported a case of complete achlorhydria with slow emptying of the stomach due apparently to a general visceral asthenia. The patient, a man of middle age, had for many years complained of occasional and somewhat trivial discomforts in the caecal region. In the autumn of 1929, extraction of his teeth was recommended, and from the date of this operation he became seriously ill. In the spring of 1930 he was bedridden, nervous, and depressed, complaining of a feeling of epigastric fullness, and discomfort in the caecal region, and also numbness and pains in the legs. A fractional gastric analysis revealed complete achlorhydria with a very high total acidity and slow emptying. An X-ray examination disclosed marked gastric atony, the stomach containing barium at the end of 24 hours. There was no pyloric deformity. Clinical examination showed definite peripheral neuritis with foot-drop and anaesthesia. The case subsequently recovered very slowly.

3 p.m. *Afternoon Session.*

1. Dr. Claude Wilson commented on *A Case of Acholuric Jaundice*, which was shown among the exhibits. The patient, a man of 49, was the sole survivor (in the third generation) of the group described by him under the title of 'Hereditary Enlargement of the Spleen' in 1890. His colour was characteristic and his spleen large and hard. The red count and haemoglobin were both around 60 per cent. Yet his health was excellent, although splenectomy had been performed.

These observations were discussed by Drs. Parkes Weber, Abrahams, and McNee.

2. Professor F. Langmead and Dr. T. C. Hunt (introduced) reported *The Results in 75 Patients subjected to the Water Test of Kidney Function.* After a dose of 30 oz. of fluid normal excretion lay between 25 and 35 oz. of urine in four hours. 11 patients passed more than 35 oz. in 4 hours, of whom all but two had definite kidney disease. 36 patients showed water-retention, of whom 24 excreted less than 20 oz. in 6 hours: in 32 of these patients kidney disease was present, and in 10 of them water-retention was the only evidence by functional tests of its presence, the range of urea concentration and the blood urea tests being normal.

The water test often offers the earliest evidence of kidney impairment; it does not indicate accurately the severity of impairment, which shows itself sometimes by an excessive excretion (an early stage) or by water-retention. The specific gravity and the respective hourly volumes of the specimens must also be considered. It is not suitable when oedema is present.

3. Dr. E. P. POULTON and Dr. J. H. RYFFEL (introduced) on *Rate of Urea Output as a Test of Renal Function.* A number of normal students have been investigated, using the ordinary technique of the urea concentration test. The results on patients who had no kidney disease have also been used. It has been found that the percentage of urea varies very nearly inversely as the hourly volume of the urine after the test, and that the rate of urea output remains fairly constant and this value instead of urea concentration should be used in estimating kidney function. Under these circumstances it appears that in hydraemic nephritis the excretion of urea is imperfect.

Drs. Graham and Ellis joined in the discussion.

4. Dr. R. D. GILLESPIE discussed *Mental Symptoms in Physical Disease.* The term organic and functional are often confused. 'Functional' and 'psychogenic' are not synonymous. The one is a phenomenological, and the other a causal category. While there is no specific relationship between types of physical illness and the mental syndrome resulting, many different physical noxae producing a small number of mental syndromes, most of the latter are virtually specific for physical disease in general, i.e. are rarely the result of anything but physical disease. The mental syndromes resulting from the physical disease are divisible according to their course and types into acute and chronic varieties. The acute varieties are confusion, in the sense of impairment of comprehension and memory with disorientation, delirium; and of much rarer incidence, a disoriented dream-state. The first two are so constantly associated with the presence of a physical noxa, and so comparatively rarely result from psychological causes that their presence is nearly always diagnostic of a physical cause.

The chronic varieties of mental disorder resulting from physical disease are (1) simple dementia, (2) Korsakov's syndrome, and (3) the 'hyperaesthetic-emotional state of weakness' of German authors. The differentiation of the latter from a psychogenic neurasthenia can be made partly on differences in the symptoms and partly on historical and similar collateral evidence.

Occasionally one encounters instances of manic-depressive, schizophrenic, paranoid, and oriented hallucinatory reactions during the course of a physical disease, or in its sequel. These must be considered to be trends based on factors of personality, inherited and acquired ('complexes'), released by the general failure of inhibition produced by the physical disease.

Dr. Travers Smith discussed these observations.

5. Dr. CRIGHTON BRAMWELL recorded *Some Observations on Marathon Runners.* He had examined a group of 32 Marathon runners during the period of training, at the Olympic Games in Amsterdam. These men had relatively larger hearts than other athletes, their resting heart rate was slower and their blood-pressure relatively low. They were men of a phlegmatic temperament. The average age of the group was 27, and only one man under 25 did well in the race. Blood-sugar estimations after the race showed in some instances a definite hypoglycaemia, and a shortage of glycogen appeared to be an important factor in determining the limits of their endurance. Five of the first seven places in the race were taken by men in the group examined; but there were no special clinical features in the cardiovascular mechanism which would serve to differentiate these successful athletes from other members of the group.

Drs. Abrahams, Claude Wilson, and Simey recorded observations on training for athletics and runners.

6. Dr. HENRY COHEN spoke on *Brucella Abortus Infection in Man.* He outlined briefly the evidence which led to the recognition of (1) the relationship between M. melitensis and the B. abortus of Bang; and (2) the occurrence of Brucella abortus infection in man. The main clinical types observed were (i) the classical undulant form; (ii) the arthritic; (iii) the genit l; (iv) the abdominal, and (v) the 'catarrhal jaundice' type.

He discussed the diagnosis from the standpoint of blood and urine cultures: agglutinations; and skin reactions, and emphasized the necessity for recognizing the existence of this disease as a possible cause of obscure pyrexias.

Drs. Synge and A. G. Anderson referred to cases.